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Sofosbuvir, Velpatasvir, and Voxilaprevir for Treatment of Recurrent Hepatitis C Virus Infection After Liver Transplantation

Maria G. Cardona-Gonzalez,¹ Jason D. Goldman,^{1,2} Lawrence Narayan,¹ Diana M. Brainard³, and Kris V. Kowdley¹

There are limited data on direct-acting antiviral (DAA) treatment options for previously treated patients with recurrent genotype 3 (GT3) hepatitis C virus (HCV) after liver transplantation. Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is currently approved for treatment of HCV in patients with prior treatment with DAAs. We report the first published experience using SOF/VEL/VOX after liver transplantation for a DAA-experienced patient with severe hepatitis due to early recurrent GT3 HCV. The patient was treated with SOF/VEL/VOX that was extended to a total duration of 16 weeks and was intensified with ribavirin (RBV) starting at week 8 due to persistent viremia during treatment. Sustained virologic response at 12 weeks (SVR12) after treatment completion was achieved. SOF/VEL/VOX was well tolerated, and immediate drug–drug interaction (DDI) with tacrolimus (TAC) was not evident. Due to improvement in liver metabolic function with increasing TAC clearance, TAC dose adjustment was required throughout the treatment course. *Conclusion:* SOF/VEL/VOX can be considered for treatment of recurrent HCV after transplantation. Further study is needed to establish safety and efficacy and define treatment duration in difficult-to-treat populations. (*Hepatology Communications* 2018;2:1446-1450).

Direct-acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) infection have dramatically changed the landscape to treat recurrent HCV after orthotopic liver transplantation (OLT). Drug–drug interactions (DDIs) may influence the use of DAAs for treatment of HCV post-OLT and may pose challenges to successful dosing of DAAs or anti-rejection medications. SOF/VEL/VOX is currently approved for treatment of HCV in patients with prior treatment with DAAs.⁽¹⁾ However, to our knowledge, use of this regimen has not been described

in the post-OLT setting. We report our experience in using sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) to treat a DAA-experienced patient with severe hepatitis due to early recurrent genotype 3 (GT3) HCV.

Patient and Methods

CASE REPORT

A 61-year-old male with a past medical history of diabetes, hypertension, and chronic back pain was

Abbreviations: AASLD–IDSA, American Association for the Study of Liver Diseases–Infectious Disease Society of America; ALT, alanine aminotransferase; CYP3A4, cytochrome P450 3A4; DAA, direct-acting antiviral; DDI, drug–drug interaction; EOT, end of treatment; GLE/PIB, glecaprevir/pibrentasvir; GT3, genotype 3; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; OLT, orthotopic liver transplantation; P-gp, permeability glycoprotein; POD, postoperative day; RBV, ribavirin; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR, sustained virologic response; TAC, tacrolimus.

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diagnosed with GT3 HCV in 1995. By January 2014, he had developed biopsy-proven cirrhosis; he had interleukin (IL) 28B GT CT.

The patient was first treated for HCV in February 2014 with SOF and ribavirin (RBV) for 16 weeks as part of the Bosen Study.⁽²⁾ He achieved undetectable HCV RNA by week 8 through the end of treatment (EOT). However, HCV viremia recurred at 4 weeks after EOT, and he was subsequently retreated with SOF, RBV, and pegylated interferon alfa-2a for 12 weeks. The patient developed anemia, insomnia, and fatigue but completed the treatment regimen. HCV RNA was undetectable at week 8 and sustained though EOT, but again viremia recurred at 4 weeks after EOT. During both these treatments, study investigators and clinicians assessed that the patient adhered assiduously to the treatment regimen. No nonstructural protein 5B (NS5B) resistance-associated substitutions were identified using a 15% deep sequencing cutoff at the baseline and treatment failure time points for both treatment attempts. NS5A genotyping was not performed. In March 2016, the patient was found to have hepatocellular carcinoma (HCC) and was treated with radio frequency ablation and transarterial chemoembolization.

The patient underwent OLT with exception points for HCC in August 2017. The donor was a trauma victim who was not HCV infected. Baseline laboratory testing prior to OLT showed white blood cell count $12.7 \times 10^3/\mu\text{L}$, hemoglobin 14.2 g/dL, platelets $164 \times 10^3/\mu\text{L}$, normal kidney function with creatinine 1.18 mg/dL, and liver function showing total bilirubin 0.6 mg/dL, alanine aminotransferase (ALT) 200 U/L, aspartate aminotransferase 119 U/L, and alkaline phosphatase 161 U/L. Induction immunosuppression was high-dose methylprednisolone with taper, and the maintenance immunosuppression regimen included tacrolimus (TAC), mycophenolate mofetil, and prednisone. The immediate

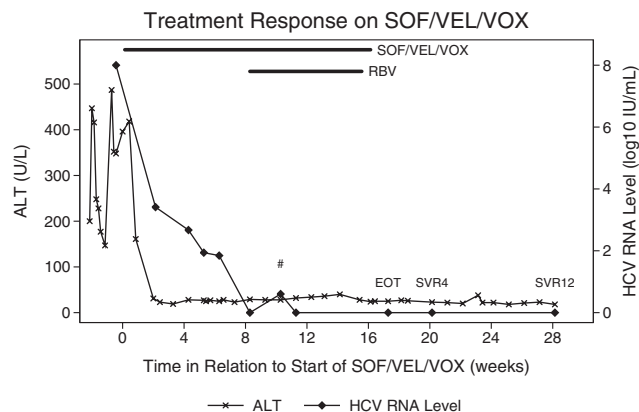


FIG. 1. Treatment response of patient on DAA therapy with SOF/VEL/VOX. # indicates an HCV RNA level that was detected (<15 IU/mL) but below the limit of linear quantitation for the assay.

postoperative course was uncomplicated, but the patient was readmitted to the hospital on postoperative day (POD)9 with elevated liver enzymes. After OLT, ALT spiked to 447 U/L on POD1 and decreased to nadir 147 U/L on POD6 but increased to 487 U/L on POD9 (Fig. 1). Total bilirubin was 3.6 mg/dL after transplant, decreased to 0.8 mg/dL on POD6, and increased only slightly to 0.9 mg/dL on POD9. Similarly, alkaline phosphatase was also not elevated. Biopsy showed portal inflammation, lymphocytic cholangitis, mild steatosis, and no evidence for fibrosis, findings not diagnostic for acute rejection. POD11 HCV RNA was >100,000,000 IU/mL, verified as GT3, confirming the diagnosis of acute allograft hepatitis due to recurrent HCV. The patient started SOF/VEL/VOX for recurrent HCV on POD15 for a planned treatment course of 12 weeks. Although data in the post-OLT setting for SOF/VEL/VOX were lacking, this regimen was

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chosen over the SOF/VEL combination⁽³⁾ due to the high efficacy of SOF/VEL/VOX ($\geq 95\%$ sustained virologic response at 12 weeks [SVR12]) in phase 3 studies in DAA-experienced patients infected with GT3 HCV.⁽¹⁾ Alternatively, options included in the American Association for the Study of Liver Diseases–Infectious Disease Society of America (AASLD/IDSA) guidelines at the time of DAA regimen initiation (August 2017) included daclatasvir (DCV) and SOF (DCV + SOF), but guidelines recommended extension to 24 weeks and addition of RBV.⁽⁴⁾ At the time of regimen selection, AASLD-IDSA guidelines did not include a recommendation for glecaprevir/pibrentasvir (GLE/PIB). Preliminary results from the MAGELLAN-2 trial of GLE/PIB in patients after OLT were not yet published but had been presented at the European Association for the Study of the Liver (EASL) 2017 international meeting. The MAGELLAN-2 trial did not enroll any participants experienced in GT3 treatment.⁽⁵⁾ In the context of no clear guidance for the multiple hard-to-treat characteristics of our GT3 patient with multiple treatment experiences, we selected SOF/VEL/VOX as the most potent and likely to be successful.

Results

After starting SOF/VEL/VOX, HCV viremia decayed rapidly with a >4 log₁₀ drop in HCV RNA by week 2 but with a slower decrease in HCV RNA through week 8 when HCV RNA was first undetectable (Fig. 1). Due to detectable viremia at treatment weeks 4 and 6, the decision was made to extend therapy to 16 weeks. At week 8 of SOF/VEL/VOX therapy, RBV was added. At week 10, HCV RNA was detectable but below the range of linear quantification for the assay (<15 IU/mL). With the addition of RBV, the patient developed insomnia, fatigue, and anemia and required blood transfusion. Antiviral treatment for HCV was completed in December 2017, and SVR was demonstrated at 4 and 12 weeks after completing treatment.

Other medications during SOF/VEL/VOX treatment included valganciclovir, zolpidem, omeprazole, furosemide, insulin, nebivolol, irbesartan, bupropion, and oxycodone. Neutropenia requiring filgrastim rescue developed in January 2018 and was ascribed to the anti-cytomegalovirus prophylaxis valganciclovir.

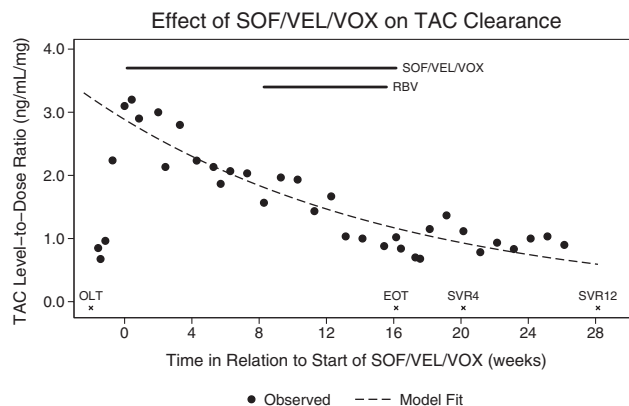


FIG. 2. Effect of SOF/VEL/VOX on TAC clearance and liver metabolic function. The TAC level was normalized to the daily dose given 1 day prior to TAC level measurement. The TAC level-to-dose ratio is inversely correlated with TAC clearance and liver metabolic function (see text).⁽⁹⁾ An exponential decay curve was fit to the TAC level-to-dose data, excluding the three normalized levels immediately after OLT, as these were non-steady-state measurements, and preceding initiation.

The immunosuppression strategy was not adjusted *a priori* before DAA treatment with SOF/VEL/VOX. TAC trough levels were monitored weekly and adjusted to goal levels per post-OLT protocol. Initially, no adjustment of the TAC dose was necessary after starting SOF/VEL/VOX; however, over the course of the DAA treatment, TAC dose was slowly and progressively increased in response to weekly trough levels and the immunosuppression protocol. At DAA initiation, the daily dose was 2 mg, and at EOT the daily dose was 5 mg, a 150% increase over the course of SOF/VEL/VOX treatment. A normalized metric of TAC dosing (TAC level-to-dose ratio) decreased over the course of treatment (Fig. 2), indicating increasing TAC clearance.

Discussion

To our knowledge, we describe the first use of the pan-genotypic DAA therapy SOF/VEL/VOX for treatment of recurrent HCV after OLT. For recurrence in persons with GT3 HCV infection, AASLD-IDSA guidelines recommend GLE/PIB or DCV + SOF; however, data for treatment-experienced persons in this setting are lacking.⁽⁴⁾ The MAGELLAN-2 study of GLE/PIB in posttransplant patients did not enroll any GT3 treatment-experienced participants.⁽⁵⁾

Although both GLE/PIB and DCV have potential to interact with TAC through weak cytochrome P450 3A4 (CYP3A4) inhibition and permeability glycoprotein (P-gp) inhibition, respectively, neither regimen has been studied in DAA-experienced patients with GT3 HCV in the posttransplant setting. Treatment with SOF/VEL/VOX was selected from the available choices at the time due to our perception that this regimen would be the most potent in the context of multiple prior treatment failures and given the relative paucity of real-world information with GLE/PIB or DCV + SOF + RBV in the posttransplant setting for GT3 HCV infection after prior DAA treatment failures. At the time of regimen selection (August 2017), there was no clear option, and published data on experience with DAAs remain scant in difficult-to-treat populations, such as posttransplant, GT3, and treatment experienced. Guidelines from AASLD-IDSA⁽⁴⁾ concur with guidelines from EASL⁽⁶⁾ in listing SOF/VEL with weight-based RBV as an alternative regimen for post-OLT treatment in GT3 patients. Although recent data have suggested excellent outcomes for SOF/VEL without RBV in patients with GT3 and post-OLT HCV recurrence, we selected SOF/VEL/VOX on empirical grounds as the most potent regimen most likely to achieve cure given the paucity of data on patients similar to ours with DAA treatment experience, a history of HCC, and concurrent immunosuppression.⁽⁷⁾

Although treatment with SOF/VEL/VOX was well tolerated and effective, treatment extension to 16 weeks and intensification with the addition of RBV were undertaken empirically to increase the probability of a successful outcome. Initial response to SOF/VEL/VOX showed rapid first-order kinetics and slower second-order kinetics. Detectable HCV RNA at weeks 4 and 6 prompted therapy extension of SOF/VEL/VOX and intensification with RBV. Recurrent, low-level viremia (below the linear detection limit of the assay) was observed during the treatment course. Although common during the interferon era, data have not supported using response-guided therapy (i.e., treatment decisions based on viral decay kinetics) with DAAs.⁽⁸⁾ Nevertheless, the patient's initial viral load of >10,000,000 IU/mL and viremia to 6 weeks was not typical of the patients studied in clinical trials, and therefore direct application of these data to our patient's unique circumstances did not seem appropriate.

A major challenge of HCV treatment after OLT is the possible DDIs with immunosuppressive therapy. This is particularly evident with calcineurin inhibitors, as coadministration with SOF/VEL/VOX and cyclosporine has been shown to substantially increase the plasma concentration of VOX in healthy adults with no studies assessing its safety. As a result, the coadministration of SOF/VEL/VOX with cyclosporine is not recommended. Our patient was given TAC, which is a substrate for both CYP3A4 and P-gp and also a weak inhibitor for P-gp. Potential DDIs of TAC with SOF/VEL/VOX have not been systematically studied, although significant interactions requiring empiric dose modification are not anticipated. VOX is a substrate and inhibitor of P-gp and solute carrier organic anion transporter family member 1B1 (OATP1B1) and OATP1B3 and is slowly metabolized by CYP3A4. Careful monitoring of the TAC dose after initiation of SOF/VEL/VOX showed no immediate change in either the TAC level or TAC level-to-dose ratio, suggesting an absence of clinically significant DDIs. However, the TAC level-to-dose ratio continuously decreased over the course of SOF/VEL/VOX treatment (Fig. 2). This ratio is inversely related to liver metabolic function or clearance of TAC and therefore liver enzymatic function.⁽⁹⁾ Clearance of TAC and liver metabolic function increased over the course of SOF/VEL/VOX treatment. Our experience confirms that *a priori* TAC dose adjustment is not necessary, but continued close monitoring of TAC concentration during DAA therapy with SOF/VEL/VOX is necessary to avoid subtherapeutic TAC dosing and the potential for allograft rejection. These findings suggest that acute hepatitis from recurrent HCV after OLT affects hepatic metabolic function and can be reversed with treatment of recurrent HCV.

DAAs have great promise for alleviating the morbidity and mortality of recurrent HCV after OLT. Difficult-to-treat populations exist, such as GT3 and treatment-experienced persons. SOF/VEL/VOX represents a potent pan-genotypic regimen that proved effective in this situation of multiple treatment failures and did not show clinically significant DDIs with TAC and other coadministered medications. Response-guided treatment in the DAA era may still be an important tool in difficult-to-treat persons. Because this was a single case, it is important to state that we cannot infer safety and efficacy when applying to a wider population.

Specifically, we cannot conclude from our experience if SOF/VEL/VOX alone for 12 weeks would have proved effective without RBV intensification or duration extension to 16 weeks. Additional data are needed in the posttransplant setting to further characterize the safety and efficacy of this regimen in this vulnerable population with high unmet medical need.

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