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Letter to the Editor: Successful treatment of multidrug resistant hepatitis C after >12 months of continuous therapy with direct-acting antivirals

Sheri Trudeau
Henry Ford Health, STRUDEA1@hfhs.org

Vivek Mendiratta
Henry Ford Health, vmendir2@hfhs.org

Yara Dababneh
Henry Ford Health, ydababn1@hfhs.org

Jennifer Hollingsworth
Henry Ford Health, jhollin1@hfhs.org

Stuart C. Gordon
Henry Ford Health, sgordon3@hfhs.org

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CORRESPONDENCE

Letter to the Editor: Successful treatment of multidrug resistant hepatitis C after >12 months of continuous therapy with direct-acting antivirals

To the editor, In the era of highly effective direct-acting antiviral (DAA) therapies for chronic hepatitis C virus (HCV) infection, the <5% of patients who experience treatment failure represent a clinical challenge. Current guidelines recommend a 16-week course of treatment with glecaprevir (GLE)/pibrentasvir (PIB) plus sofosbuvir (SOF) and ribavirin (RBV) for patients who are multidrug resistant and otherwise difficult to treat.[1] There are no clinical data to support treatment decisions for patients who fail this last line of therapy. We present the case of a patient with a history of multiple failed treatments who ultimately achieved sustained virological response (SVR) after an extended course of DAA regimens.

BACKGROUND

A 71-year-old man with HCV genotype (GT) 1a and cirrhosis had previously failed treatments that included pegylated interferon (IFN), 24 weeks of SOF/ledipasvir, 12 weeks of GLE/PIB with RBV (MAGELLAN-2 trial)[2], 16 weeks of GLE/PIB/RBV plus SOF (MAGELLAN-3; the only one of 23 trial participants to not achieve SVR)[2], and 12 weeks of SOF/velpatasvir (VEL)/voxilaprevir with RBV. The patient was adherent with all treatments. Testing for resistance-associated substitutions (RAS) during the MAGELLAN-2 and -3 trials detected relevant changes in both NS3 (A156V) and NS5A (Q30K and Y93H) regions (as detailed in Wyles et al.[2]).

EXTENDED TREATMENT

Failure to respond to multiple DAA salvage regimens led to the decision to initiate a long-term course of antivirals with the goals of prolonged viral suppression and symptom reduction. Figure 1 illustrates the type and duration of treatments provided; insurance limitations, and patient cost concerns necessitated the use of several different regimens, including those made available through the generosity of a private donor.

As shown, treatment began with an 8-week course of SOF/daclatasvir+RBV and IFN. During this course of therapy, the patient contracted COVID-19; RBV and IFN were paused for 2 weeks because of patient fatigue, then restarted and maintained (as tolerated) throughout the following treatment regimens. At week 4 post-treatment initiation, the patient had an undetectable viral RNA level; tests repeated at 2–4-week intervals for the duration of treatment remained negative. At week 12, the regimen was changed to SOF/VEL. At week 17, we initiated an extended (26-week) course of GLE/PIB; 13 weeks into this course (week 30 overall), SOF was added to the regimen. This combined GLE/PIB/SOV regimen was continued for 13 weeks. Finally, at week 43, treatment reverted to SOF/VEL for 13 weeks. All treatment ended at week 56.

The patient underwent follow-up HCV RNA testing at 6, 13, and 24 weeks after completion of treatment. Levels remained "undetectable," fulfilling criteria for SVR24.

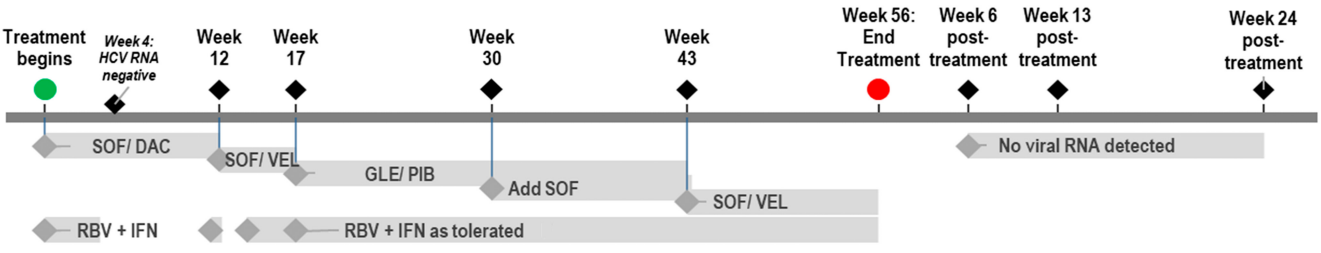

FIGURE 1 Timeline of treatment and hepatitis C virus (HCV) RNA testing. DAC, daclatasvir; GLE, glecaprevir; IFN, pegylated interferon; PIB, pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

DISCUSSION

We present what we believe is the first case description of SVR24 in a patient with multiple NS3 and NS5A RASs, coupled with a history of both on-treatment viral breakthrough and post-treatment relapse across multiple extended courses of the currently recommended salvage DAA regimens. The goal of long-term viral suppression in order to ultimately achieve SVR may represent a viable option for these rare patients with intractable HCV infections.

Treatment guidelines for patients with treatment-resistant infections are based largely on limited case series or anecdotal reports, as there are too few patients available to support additional clinical trials. Given that our patient had failed multiple extended courses of currently recommended therapies for re-treatment after DAA treatment failure, there was a complete absence of evidence-based options to guide treatment selection. Our goal, based on clinical judgment, was to achieve long-term viral suppression even if this required that the patient remain on-treatment indefinitely.

To achieve this aim, insurance and financial constraints necessitated—perhaps fortuitously—the use of multiple different regimens. Previous testing in our patient detected RASs that are strongly associated with resistance to GLE/PIB in GT1a infections.[3] We initiated treatment with two SOF-based regimens and achieved undetectable viral loads before transitioning to GLE/PIB. The patient also took pegylated IFN and RBV intermittently for the entire duration of treatment. Although there is evidence that adjuvant RBV increases the rate of SVR after DAA treatment failure,[4] the potential beneficial role of IFN can only be speculated upon. It is also possible that some refractory cases of HCV may simply require a considerably longer span of treatment to successfully eliminate the virus.

Our patient—despite a history of failing to achieve SVR across both IFN and multiple DAA regimens—was finally able to achieve SVR24 after roughly 13 months of continuous DAA treatment coupled with RBV and IFN as tolerated. It is possible, therefore, that extending treatment length beyond current recommendations may be necessary to successfully induce a durable response among patients with multiple RASs and previous treatment failures.

AUTHOR CONTRIBUTIONS

Conceived and designed the analysis: Sheri Trudeau and Stuart C. Gordon. Collected the data: Vivek Mendiratta, Jennifer Hollingsworth, Yara Dababneh, and Stuart C. Gordon. Contributed data or analysis tools: Sheri Trudeau, Vivek Mendiratta, Jennifer Hollingsworth, Yara Dababneh, and Stuart C. Gordon. Wrote the paper: Sheri Trudeau and Stuart C. Gordon.

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CONFLICT OF INTEREST

Nothing to report.

Sheri Trudeau[1]
Vivek Mendiratta[2]
Yara Dababneh[3]
Jennifer Hollingsworth[2]
Stuart C. Gordon[2,4]

[1]*Department of Public Health Sciences, Henry Ford Health, Detroit, Michigan, USA*
[2]*Department of Gastroenterology and Hepatology, Henry Ford Health, Detroit, Michigan, USA*
[3]*Department of Internal Medicine, Henry Ford Health, Detroit, Michigan, USA*
[4]*School of Medicine, Wayne State University, Detroit, Michigan, USA*

Correspondence
Stuart C. Gordon, Department of Gastroenterology and Hepatology, Henry Ford Health, 2799 W Grand Blvd, Detroit, MI 48202, USA.
Email: sgordon3@hfhs.org

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