Sustained Virologic Response for Chronic Hepatitis C Infection After 27 Days of Treatment with Sofosbuvir and Ribavirin

Eric G. Meissner,[1] Amy Nelson,[1] Miriam Marti,[1] Henry Masur,[2] Anu Osinusi,[1,3] and Shyam Kottilil[1]

[1]Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, and [2]Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, Maryland; [3]Division of Infectious Diseases, Institute of Human Virology, University of Maryland Medical School, Baltimore, Maryland

Successful treatment of chronic hepatitis C virus infection can now be achieved using direct-acting antiviral agents without interferon. In this report, we present a patient who achieved a sustained virologic response after 27 days of treatment with sofosbuvir and ribavirin. It is imperative to identify factors that allow for shorter treatment times in some individuals.

Keywords. hepatitis C virus; interferon-free treatment; sofosbuvir; sustained virologic response.

Approximately 170 million people worldwide have chronic hepatitis C virus (HCV) infection, which can progress to liver cirrhosis and hepatocellular carcinoma if left untreated [1]. Although treatment has typically required the use of interferon (IFN)-α-containing regimens, clinical trials have demonstrated efficacy and tolerability of an array of IFN-free, directly acting antiviral (DAA) regimens [2, 3]. The minimal treatment duration using DAA drug combinations needed to achieve a sustained virologic response (SVR) is unknown, but it is likely to differ based on host, viral, and drug combination variables. For example, treatment of genotype-3 chronic HCV infection with sofosbuvir, an inhibitor of the HCV NS5B RNA polymerase, and ribavirin in the FUSION trial revealed a marked increase in the rate of SVR when treatment was extended from 12 to 16 weeks, and these results were noted in patients with cirrhosis (12 weeks, 19%; 16 weeks, 61%) and without cirrhosis (12 weeks, 37%; 16 weeks, 63%) [4].

It is also conceivable that the corollary is true. For treatment regimens yielding SVR rates over 90%, some participants are likely to receive more medication than is necessary to achieve SVR. Shorter courses of therapy have obvious advantages in terms of adherence, cost, and minimizing potentially toxicity.

In this study, we report a patient who achieved SVR after receiving only 27 days of therapy with sofosbuvir combined with weight-based ribavirin, which is a much shorter duration than the recommended 24 weeks of treatment.

CASE HISTORY

A 50-year-old white female tested positive for HCV infection in 1996 while in treatment for substance abuse. She was observed to have active disease in 2006 with HCV genotype 1a and an HCV viral load of 12 100 IU/mL. She had deferred treatment over concern for medication side effects, and she had declined a staging liver biopsy in the absence of a treatment plan. She presented to the National Institutes of Health (NIH) in early 2012 for participation in a phase 2 clinical trial investigating sofosbuvir with weight-based or low-dose ribavirin for 24 weeks to treat chronic HCV infection (NCT01441180) [5]. At screening, she endorsed anxiety about the potential staging liver biopsy, as well as the frequent blood draws required as part of the study, but gave informed consent for the study.

She had a history of using intranasal cocaine, marijuana, LSD (lysergic acid diethylamide), narcotics, and a year of intravenous drug use in 1992, but she had been free of substance use since 1996. She also had a history of depression and was taking citalopram under the guidance of a therapist she visited routinely.

Her staging liver biopsy during screening for the trial revealed a histologic activity index inflammation score of 11/18 and an ISHAK fibrosis score of 0/6 with no steatosis. Pretreatment aspartate aminotransferase (AST) level was 52 U/L, alanine aminotransferase (ALT) was 146 U/L, and her pretreatment viral load was 833 000 IU/mL. She had a favorable *IFNL4* genotype as measured by the rs12979860 (CC) and rs368234815 (TT/TT) nucleotide variants [6]. After signing the NIH/National Institute of Allergy and Infectious Diseases Institutional Review Board-approved informed consent, she was randomized to the weight-based ribavirin arm, receiving 400 mg of ribavirin in the morning, 600 mg of ribavirin at night, combined with 400 mg of daily sofosbuvir [5]. The trial

Received 25 March 2014; accepted 31 March 2014.

Correspondence: Eric Meissner, MD, PhD, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, 10 Center Drive, Building 10, Room 11N204, Bethesda, MD 20892. E-mail: eric.meissner@nih.gov.

Open Forum Infectious Diseases
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2014.

DOI: 10.1093/ofid/ofu013

was conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association.

During inpatient admission for a viral-kinetic pharmacokinetic substudy at initiation of the protocol, she reported a history of anxiety associated with situational anticipation, which she experienced in the context of this elective hospital admission. As her visits continued, anxiety at the time of phlebotomy persisted with subsequent laboratory draws. She made verbal comments connecting the phlebotomy procedure to former unpleasant memories for her, and she was advised that she could discontinue the study if her symptoms became a concern for her, but she reported they were tolerable and continued on the study.

On day 28 of treatment, she called a member of the study team and reported that she could no longer continue the study due to her anxiety with frequent blood draws and needle phobia. She presented the next day for an end of treatment visit, having stopped the study medications the day before, but declined a blood draw at that visit. Pill counts revealed that she had taken 27 doses of sofosbuvir and had missed a half-day of ribavirin (600 mg). She initially agreed to come for follow-up visits to monitor her response to treatment, but she called a week later to inform the study team she would not be returning for any subsequent visits and was removed from the trial.

Serial viral load measurements revealed a precipitous drop on therapy (Figure 1A), in conjunction with normalization of serum markers of hepatic inflammation (AST/ALT; Figure 1B); however, at the time of her last blood draw (day 21), virus was still detectable in her serum.

Fifteen months later, she called the study team and reported an undetectable HCV viral load measured by an outside physician with no interim use of HCV treatment medications. Six weeks after this call, she returned to the NIH for a one-time blood draw, which confirmed undetectable HCV.

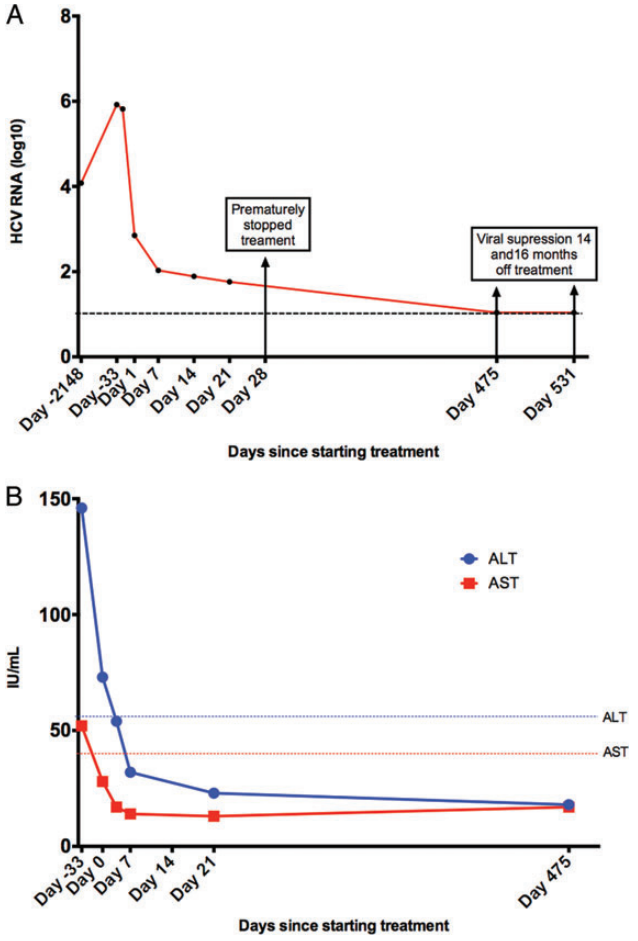

Figure 1. Virologic and hepatic inflammatory responses to treatment with sofosbuvir and ribavirin. (A) Viral load over the course of treatment. Shown is the day patient stopped study medication (day 27) as well as follow-up visits with undetectable viral load the following year. The dotted line represents the lower limit of detection. (B) Aspartate aminotransferase/alanine aminotransferase (AST/ALT) decline on therapy. Dotted lines represent the upper limit of normal for AST and ALT as indicated. HCV, hepatitis C virus.

DISCUSSION

This patient who was chronically infected with HCV achieved SVR with 27 days of sofosbuvir and weight-based ribavirin. Her course emphasizes that the duration of therapy needed to achieve SVR for HCV infection may be much shorter in some individuals than the courses used in published trials. It is possible that the necessary duration to achieve SVR will depend on the potency of the regimen used (drug factors) as well as host factors, such as the degree of fibrosis and immune status, and viral factors, such as genotype and the presence of viral polymorphisms or resistance mutations. A short course of sofosbuvir and ribavirin is clearly not effective for most patients, because 17 of 54 patients who completed 24 weeks of therapy with sofosbuvir and weight-based or low-dose ribavirin in this trial experienced treatment relapse, and regimen adherence did not seem to be a factor [5]. These discrepant responses to therapy support a strong imperative for scientific exploration of differential treatment responses to DAA therapy.

Previous models of HCV have suggested a minimum necessary treatment duration as short as 7 weeks based on viral decay modeling [7]. This case suggests that active contribution of the host immune system to eradicate residual virus may allow for shorter treatment duration in some patients. Although this patient had a favorable host *IFNL4* genotype, she also had negative predictors of favorable treatment outcome to traditional IFN-based therapy, including elevated body mass index and high baseline viral load [5, 8]. The ability to identify biomarkers distinguishing the outcome of this patient from the 17 patients who relapsed would have important ramifications for allocation of medication in resource-limited settings in the developing

world, as well as in the developed world where the cost of newly available regimens is substantial. This case study emphasizes the potential role of host factors in aiding HCV clearance, which is often not considered with the use of potent DAA regimens.

This report also illustrates both the challenge and the opportunity of DAA-based therapies. Although the regimen was well tolerated and this patient did not experience adverse events clearly attributable to the medications, she experienced a flare in prior symptoms of anxiety and depression associated with blood draws conducted as part of the trial. Although the frequency of visits and blood draws in this investigational study was greater than would be needed in a real-world setting, retention in care and adherence will remain important challenges, particularly in patients who may have ongoing issues related to substance abuse or with mental health.

It is likely that in patients such as the one described here, a contribution from the host could allow for shortened treatment duration even in the context of a less potent antiviral regimen. Hence, assessment of biological correlates in larger cohorts of patients undergoing treatment is required to help guide the possibility of individualized treatment. If these correlates can be defined, HCV therapy with DAA regimens could become more affordable and effective. Characterizing host factors that facilitate faster clearance of HCV and allow shorter duration of treatment are critical for attempts to control the epidemic globally.

Acknowledgments

Financial support. This research was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Allergy and Infectious Diseases.

Potential conflicts of interest All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology **2013;** 57:1333–42.
2. Liang TJ, Ghany MG. Current and future therapies for hepatitis C virus infection. N Engl J Med **2013;** 368:1907–17.
3. Casey LC, Lee WM. Hepatitis C virus therapy update 2013. Curr Opin Gastroenterol **2013;** 29:243–9.
4. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med **2013;** 368:1867–77.
5. Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA **2013;** 310:804–11.
6. Prokunina-Olsson L, Muchmore B, Tang W, et al. A variant upstream of IFNL3 (IL27B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. Nat Genet **2013;** 45:164–71.
7. Guedj J, Perelson AS. Second-phase hepatitis C virus RNA decline during telaprevir-based therapy increases with drug effectiveness: implications for treatment duration. Hepatology **2011;** 53:1801–8.
8. Meissner EG, Bon D, Prokunina-Olsson L, et al. IFNL4-DeltaG genotype is associated with slower viral clearance in hepatitis c, genotype-1 patients treated with sofosbuvir and ribavirin. J Infect Dis **2014**. PMID: 24367041.