

Durable Sustained Virologic Response After Oral Directly Acting Antiviral Therapy Despite Immunosuppressive Treatment

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Treatment for hepatitis C has evolved from interferon-based therapy to all oral, directly acting antiviral (DAA) therapy. The influence of immunosuppression on maintaining sustained virologic response (SVR) in patients who have been treated with these directly acting agents is unknown. In this study, we report sustained hepatitis C virus (HCV) suppression in 3 patients undergoing various immunosuppressive treatments after achieving SVR with DAA therapy. Three patients, who were enrolled in 1 of 2 single-center National Institutes of Health clinical trials, achieved SVR12. Each patient had undergone between 6 and 24 weeks of DAA therapy with or without ribavirin. Immunosuppression was varied among the 3 patients. Therapy included adalimumab, carboplatin/irinotecan, or capecitabine. In all 3 cases, patients maintained HCV RNA levels below detection after immunosuppression. All patients had undetectable viral load and normalized liver-related enzymes during immunosuppressive therapy. This report suggests that SVR as a result of novel DAA therapy is durable and likely not affected by immunosuppressive therapy. Larger studies are required to confirm these results, but findings are promising for the treatment of large numbers of HCV-infected patients who may require subsequent immunosuppressive or immunomodulating therapies.

Keywords. DAA; HCV; immunosuppression; SVR.

Hepatitis C virus (HCV) is estimated to chronically infect 170 million individuals worldwide and 3.2 million persons in the United States [1]. Left untreated, up to 25% of patients will develop liver cirrhosis and/or hepatocellular carcinoma [2, 3]. Treatment efficacy is measured by sustained virological response (SVR)12 and is defined as undetectable plasma HCV RNA level after 12 weeks of therapy. Historically, when treating with interferon (IFN)-based therapy, achieving SVR has been highly associated with host immune factors including IL28B and IFN λ 4 genotype [4, 5]. Previous studies have described increased HCV treatment failure

[6] and even treatment relapse after achieving SVR [7] in patients who received IFN therapy and subsequently underwent immunosuppression. This suggests an influence of immune mediators on treatment response and/or the presence of residual or persistent reservoirs of HCV even after achieving SVR [8, 9].

In a recent study, IFN and ribavirin-free regimens of combination directly acting antivirals (DAAs) have shown improved efficacy and tolerability compared with IFN-containing regimens, and they have become the standard of care for treatment of HCV genotype (GT)-1 [10]. However, few patients who received these new DAA agents have subsequently undergone immunosuppressing or immune-modulating therapies. Although immune-modulating and chemotherapeutic agents have been described to increase HCV load and rates of liver fibrosis progression [3], the impact of immunosuppression on HCV in patients who have already achieved SVR after treatment with DAAs is unknown [3]. As the number of patients with hepatitis C receiving

Received 10 March 2015; accepted 10 June 2015.

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Open Forum Infectious Diseases

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DOI: 10.1093/ofid/ofv091

host immune-suppressing or immune-modulating therapies during cancer treatment, organ transplantation, and autoimmune disease management grows, understanding the impact of these medications on concomitant HCV treatment outcomes has become important. This is especially true in patients with chronic HCV who receive liver transplantation (LT). Because immunosuppression after LT is a necessity, evaluating the use of DAA to prevent recurrent HCV infection is imperative.

This case series outlines the details of 3 patients who required immunosuppressive therapy shortly after completion of oral DAA regimen for HCV. In this series, SVR was maintained for all 3 patients even after immunosuppressive treatment.

CASE SERIES

One hundred ten patients were enrolled in 2 National Institute of Allergy and Infection Diseases (NIAID) clinical trials at the National Institutes of Health (NIH) evaluating DAA therapy alone for the treatment of HCV. One hundred seven (97%) of those patients achieved SVR12. Three patients were identified who received treatment with immunosuppressive or immunomodulatory agents after treatment completion. Both trials were conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association, and all patients signed NIH/NIAID Institutional Review Board-approved informed consent. Hepatitis C virus RNA was measured using the Abbott HCV RNA Assay with a published lower limit of detection of 12 IU/mL.

Case 1

A 50-year-old African American male with rheumatoid arthritis was diagnosed with HCV infection in 1998 during standard

screening. He presented to the NIH in 2013 for participation in a phase 2 clinical trial investigating sofosbuvir, ledipasvir with GS-9451 for 6 weeks to treat chronic HCV infection. Hepatitis C virus GT during screening was 1a with a viral load of 10 526 493 IU/mL. Liver biopsy in 2013 showed a histologic activity index (HAI) inflammation score of 9/18 and an ISHAK fibrosis score of 0/6 with trace steatosis. Pretreatment aspartate aminotransferase (AST) level was 32 U/L, and alanine aminotransferase (ALT) level was 56 U/L. The patient was found to have an unfavorable IL28B (rs12979860 [TT]) and *IFNL4* GT (rs368234815 [Δ G/TT]).

The patient had a history of severe rheumatoid arthritis, diagnosed 1.5 years prior, with bilateral hand, arm, and leg pain. He required hydroxychloroquine 200 mg twice daily and methylprednisolone 8 mg daily, as well as tramadol 50–100 mg daily and sulfasalazine 1000 mg twice daily for pain. He also had a history of positive purified protein derivative skin test, for which he completed 9 months of isoniazid treatment. In addition, he had a history of using intravenous and intranasal heroin and intranasal cocaine from 1990 to 2007, but he had been substance free since that time.

The patient completed 6 weeks of therapy with sofosbuvir, ledipasvir (400/90 mg combination pill), and GS-9451 (protease/NS3/4 inhibitor, 90 mg). Approximately, 1 week after completion of therapy, the patient developed painful and swollen metacarpophalangeal joints and proximal interphalangeal joints as well as bilateral elbow and knee pain. The patient's rheumatologist recommended treatment with the addition of tumor necrosis factor (TNF) inhibitor adalimumab. The effect of a biologic such as adalimumab on the risk of HCV relapse was unknown, so the decision was made, in consultation with the patient's rheumatologist, to defer treatment until after the

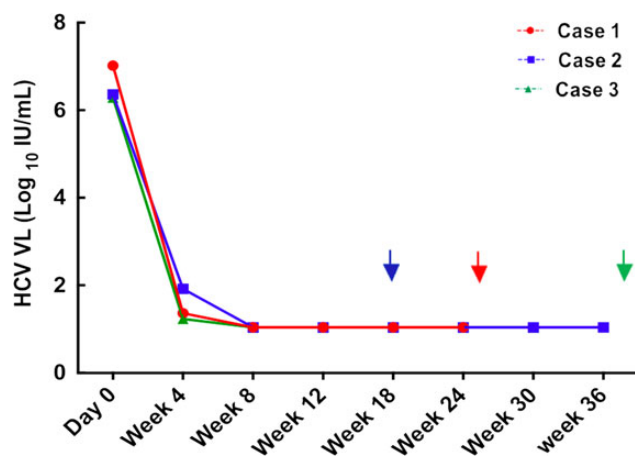


Figure 1. Hepatitis C virus viral load during and posttreatment course. Arrows indicate when immunosuppression started: in case 1 (red), week 27; in case 2 (blue), week 18; in case 3 (green), week 48.

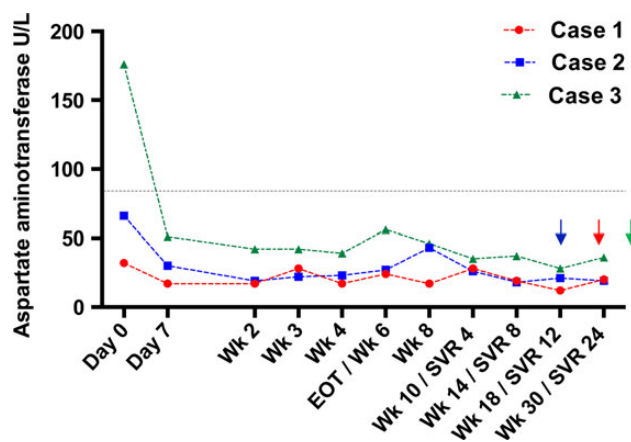


Figure 2. Aspartate aminotransferase during and posttreatment course. Arrows indicate when immunosuppression started: in case 1 (red), week 27; in case 2 (blue), week 18; in case 3 (green), week 48. Abbreviations: EOT, end of treatment; SVR, sustained virologic response.

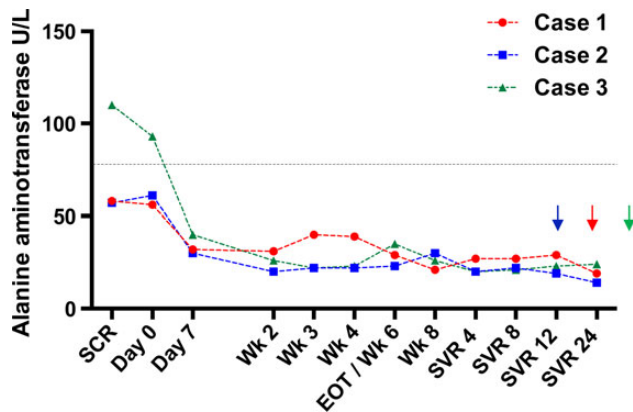


Figure 3. Alanine aminotransferase during and posttreatment course. Arrows indicate when immunosuppression started: in case 1 (red), week 27; in case 2 (blue), week 18; in case 3 (green), week 48. Abbreviations: EOT, end of treatment; SVR, sustained virologic response.

patient reached SVR12. Serial viral load measurements revealed a precipitous decline in HCV viral load with undetectable plasma HCV RNA (<12 IU/mL) at the end of treatment (Figure 1). Normalization of AST and ALT was also observed (Figures 2 and 3).

The patient achieved SVR12 with an AST level of 12 U/L and an ALT level of 29 U/L. At week 27 (21 weeks after completion of DAA HCV therapy), the patient was started on adalimumab 40 mg every 2 weeks for treatment of his rheumatoid arthritis. Follow-up visits at week 30 (24 weeks after completing therapy) and 42 (36 weeks after completing therapy) revealed that despite the addition of adalimumab, his HCV viral load remained undetectable with normal ALT and AST.

Case 2

A 57-year-old African American female was diagnosed with HCV infection in 2012 on routine screening. She presented to NIH in 2013 for participation in a phase 2 clinical trial investigating sofosbuvir and ledipasvir with GS-9669 for 6 weeks to treat chronic HCV infection. Screening laboratory test results showed infection with HCV GT-1a and an HCV viral load of 1 969 300 IU/mL. A liver biopsy in 2013 showed an HAI inflammation score of 6/18 and an ISHAK fibrosis score of 1/6 with minimal steatosis. Pretreatment AST level was 66 U/L, ALT was 59 U/L, and IL28B and IFN λ 4 GT as determined by the rs12979860 (CT) and rs368234815 (Δ G/TT), respectively.

The patient had a history of chronic obstructive pulmonary disease with an over 50-pack per year smoking history and was treated with advair, albuterol, and spiriva. She also had a history of well controlled hypertension, untreated depression with a history of delusions, and intravenous cocaine use approximately 20 years prior. She had been substance free since then. In addition, she had been treated for both active and latent tuberculosis, with 9 months and 6 months of therapy, respectively.

The patient completed 6 weeks of HCV treatment with sofosbuvir/ledipasvir (400/90 mg combination pill) and GS-9669 (nonnucleoside NS5B inhibitor, 500 mg) without difficulty, and her HCV viral load declined on therapy, with normalization of ALT and AST (Figures 1–3). The patient had an undetectable HCV viral load by week 8 of the trial, and she achieved SVR12.

At week 18 (12 weeks after completing therapy), the patient had worsening cough and difficulty lying flat. She was seen by her primary care doctor and given antibiotics and oral steroids, which improved her symptoms. Three months later, she had increased wheezing and completed another 5-day course of oral steroids. At week 33, the patient presented to the emergency department with shortness of breath and fever; she was diagnosed with pneumonia. Computed tomography of her chest also showed interval pleural and parenchymal changes concerning for malignancy. Four months later, an oncologist confirmed the diagnosis with a repeat computed tomography chest showing numerous large lesions in left lower lobe of the lung. These lesions were found to be small cell lung cancer on biopsy. The patient was started on chemotherapy (carboplatin and irinotecan) at week 53. A follow-up visit at week 54 continued to show undetectable HCV RNA viral load while on chemotherapy. The patient had progression of her lung cancer despite being on treatment, and she experienced worsening of her underlying depression with delusions. Despite multiple attempts, the patient was ultimately lost to follow up.

Case 3

A 74-year-old white female tested positive for HCV infection in 1990. She presented to NIH in 2012 for participation in a phase 2 clinic trial investigating sofosbuvir with weight-based or low-dose ribavirin for 24 weeks to treat chronic HCV infection. During screening, she was found to be infected with HCV GT-1a with a viral load of 2 363 500 IU/mL. Liver biopsy in 2010 showed a HAI inflammation score of 10/18 and an ISHAK fibrosis score of 1/6 with minimal steatosis. Pretreatment AST and ALT were 176 U/L and 93 U/L, respectively. She had both unfavorable IL28B (rs12979860 [CT]) and IFN λ 4 (rs368234815 (Δ G/TT) GTs.

The patient also had a history of right breast, triple-negative (Her2, estrogen, and progesterone receptors negative), stage IIIa adenocarcinoma diagnosed in 2009. She had completed extensive therapy including right lumpectomy with complete axillary node dissection, 6 cycles of taxotere and cytoxan chemotherapy, as well as breast and supraclavicular radiotherapy in 2010. She also had a history of myocardial infarction requiring stent placement in 2001, essential thrombocytopenia diagnosed in 2010 with positive Janus kinase-2 mutation, hypothyroidism, which was well controlled on levothyroxine, Crohn's disease not requiring medication, hypertension, hyperlipidemia, and depression.

The patient was randomized to treatment with sofosbuvir (400 mg daily) with low-dosed ribavirin arm (600 mg daily)

for 24 weeks. By week 3 of treatment, the patient had undetectable HCV viral load. Between weeks 16 and 20, the patient complained of worsening fatigue and depression—causing her to miss 5 doses of study medication. Laboratory work was done, and she was found to be anemic with hemoglobin of 11.7 g/dL. Given her history of cardiac disease, her dose of ribavirin was decreased to 400 mg daily. Hepatitis C virus treatment was completed at week 24, and she reported improved mood and fatigue.

At week 25, the patient complained of severe right lower quadrant pain. A computed tomography of the abdomen showed intestinal inflammation consistent with flare of the patient's pre-existing Crohn's disease. In addition, mixed sclerotic and lytic lesions on the iliac bones and vertebral bodies were seen, suspicious for recurrent breast cancer with bony metastasis. Breast cancer was confirmed 2 months later by bone biopsy, and the patient was initiated on capecitabine at week 48 (24 weeks after completing HCV therapy). At this time, the patient had an HCV viral load that was undetectable (SVR24). The patient continued capecitabine for 2 months and was then switched to taxotere after developing a facial rash due to capecitabine. At weeks 60 and 72, after receiving chemotherapy, the patient had undetectable HCV RNA. The patient left the study at week 72, but she returned during week 113 for a final follow up and was found to have an undetectable HCV RNA viral load and normalized ALT and AST.

DISCUSSION

In this case series, 3 patients completed treatment with IFN-sparing combinations of DAAs and then received immunosuppressive biologic or chemotherapeutic agents. There was no evidence of viral relapse at least 48 weeks after completion of DAA therapy. Although host immune factors influence relapse posttherapy with IFN-containing therapy [4, 5], the durability of SVR despite immunosuppressive therapy suggests that immune factors do not play a role in maintaining SVR after treatment with IFN-sparing therapy.

Standard therapy for HCV treatment has long included combinations of IFN and ribavirin. Although this treatment is efficacious, it can worsen autoimmune-mediated diseases [11], and its use is limited in medical and psychiatric conditions that often co-exist in patients infected with HCV. In contrast, IFN-free options such as DAA regimens have fewer contraindications, no significant neuropsychiatric risk, and are much better tolerated [10].

Although correlates of immune system function, including host IL28B or *IFNL4* GT, have been shown to predict treatment success to IFN-containing therapy [4, 5], little is known about the effect of immunosuppression on SVR. Some studies have detected residual HCV RNA in blood components of patients who achieved SVR, suggesting the possibility of occult infections [8, 9]. Hepatitis C virus relapse has been reported in patients who achieved SVR with IFN and ribavirin-containing therapy and were subsequently treated with immunosuppression [12]. A recent case series showed durability of SVR for a median of 96 months postchemotherapy in these patients treated with IFN and ribavirin who had previously achieved SVR [13].

There are several limitations to this study. First, the timing of immunosuppression was largely dictated by each patient's disease pathology. In case 1, the start of adalimumab was held until after the patient reached SVR12. This decision was made in conjunction with the patient's rheumatologist because little is known about the effect of biologics on the risk of HCV relapse. In contrast, in cases 2 and 3, chemotherapy was initiated immediately after cancer was confirmed on biopsy. However, in both of these cases, the patients had achieved SVR12 and SVR24, respectively, before the start of immunosuppression. Other limitations include the lack of repeat viral load measures after immunosuppression, as seen in case 2.

This is the first report illustrating that SVR after DAA therapy is not affected by immunosuppressive therapy. In these 3 patients treated with DAAs, SVR was maintained despite immunosuppression. All 3 of the cases had unfavorable HCV GT-1a, unfavorable host *IFNL4* GT, high HCV viral loads

Table 1. Summary of Three Cases

Characteristics of study population	Patient 1	Patient 2	Patient 3
Age at start of trial (years)	50	57	74
Baseline HCV RNA (IU/mL)	10 526 493	1 969 300	2 363 500
DAA therapy	6 wk of 400 mg sofosbuvir + 90 mg ledipasvir + 90 mg GS-9451	6 wk of 400 mg sofosbuvir + 90 mg ledipasvir + 500 mg GS-9669	24 wk of 400 mg sofosbuvir + 600 mg ribavirin
Diagnosis and IT regimen	Rheumatoid Arthritis: adalimumab, hydroxychloroquine, methylprednisone, sulfasalazine	Small cell lung cancer: 6 cycles of carboplatin and irinotecan, 1 cycle of cisplatin-etoposide	Metastatic breast cancer: 6 cycles of capecitabine, cyclophosphamide, docetaxel, doxorubicin
Weeks of IT after SVR12	9 wk	34 wk	10 wk
Latest SVR follow up after end of DAA therapy	42 wk	54 wk	113 wk

Abbreviations: DAA, directly acting antiviral; HCV, hepatitis C virus; IT, immunosuppressive therapy; SVR, sustained virologic response.

at the start of the trial, and 2 of the 3 patients were African American. Despite these negative predictors of favorable outcome, all 3 cases were found to have undetectable viral load and normalized liver-related enzymes at the endpoint of their studies (SVR12 for cases 1 and 2, SVR24 for case 3). After achieving SVR, the patients continued to have undetectable viral load despite undergoing immunosuppression in the form of chemotherapy, steroids, or inhibition of TNF (Table 1).

CONCLUSIONS

As well tolerated DAA regimens are approved and their use becomes more widespread, treatment of a broader range of patients will occur. This includes patients on immunosuppressive therapy. Larger studies are needed to confirm the durability of HCV SVR in patients treated with DAAs who also receive immunosuppression. Pending validation in larger studies, it appears that SVR after DAA therapy is not compromised by the subsequent use of immunosuppressive medications. This is a significant finding for the large numbers of HCV-infected patients who may require future immunomodulatory or chemotherapeutic medications.

Acknowledgments

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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