Successful treatment with sofosbuvir and daclatasvir plus ribavirin in acute hepatitis C-infected patient with hepatic decompensation

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Abstract: Treatment of chronic hepatitis C virus infection has evolved rapidly in recent years due to the invention of interferon-free direct antiviral agents (DAAs). However, evidence and recommendations for acute hepatitis C (AHC) virus infection by DAAs are still limited, especially for those whose disease presents with hepatic decompensation. Here, we report a case with genotype 1b AHC virus infection, complicated by hepatic decompensation and the patient received sofosbuvir and daclatasvir plus low dose ribavirin for 12 weeks. Serum hepatitis C virus RNA significantly declines after therapy and became undetectable at week 8 and it remained undetectable at 12 weeks after finishing therapy; sustained virological response was impressed. Our findings support that combination of sofosbuvir and daclatasvir plus ribavirin can be used for genotype 1b, AHC virus infection patients with overt hepatic decompensation.

Keywords: Acute hepatitis C; Direct acting antiviral agent; Hepatic decompensation

1. INTRODUCTION

Hepatitis C virus (HCV) infection is one of the leading causes of hepatic decompensation, hepatocellular carcinoma, and liver transplantation.[1–4] The prevalence of HCV infection is estimated to be around 3% worldwide and results in approximately 350 000 deaths annually.[5,6] Around 3 to 4 million people are newly infected with HCV annually, and this trend is not limited to developing countries, as 18 000 new HCV infections occur annually in the USA.[7,8] Genotype 1 (GT1) accounts for approximately 70% of all HCV infections and subgenotype 1b is predominant in Europe and Eastern Asia.[9,10]

Populations at risk for acute hepatitis C (AHC) virus infection are patients who have received blood transfusions or blood products before routine screening for HCV, intravenous drug users using nonsterile needles, healthcare workers, dialysis patients, and those involved in high-risk sexual activities.[11,12] AHC infection is infrequently diagnosed because most patients are asymptomatic. Approximately 20% to 30% of adults may develop clinical symptoms, which are usually mild and nonspecific. Onset of symptoms occurs 3 to 12 weeks after exposure. Symptoms may include malaise, weakness, anorexia, and jaundice. Jaundice appears in only 15% to 20% of acutely infected patients and fulminant liver failure is rare except in those with underlying chronic hepatitis B virus infection.[13]

Regarding the diagnosis of AHC, serum HCV RNA can be detected within 1 to 2 weeks from exposure. The level of HCV RNA rises rapidly during the first few weeks and then peaks between 10^5 and 10^7 IU/mL, followed by a peak in serum alanine aminotransferase (ALT) levels and onset of symptoms.[14] Serum ALT levels start rising 2 to 8 weeks postexposure and often reach levels more than 10 times the normal upper limits. Anti-HCV antibodies (anti-HCV), as detected by enzyme-linked immunosorbent assay, become positive (ie, anti-HCV seroconversion) around the onset of symptoms, approximately 1 to 3 months after exposure. Up to 30% of patients may have negative results for anti-HCV at the onset of their symptoms, making anti-HCV testing alone unreliable as a diagnosis instrument for AHC infection.[7]

Treatment of chronic hepatitis C (CHC) has evolved rapidly in recent years due to the invention of interferon (IFN)-free direct antiviral agents (DAA). Currently approved DAA therapy with sofosbuvir (SOF)-containing regimens has dramatically improved rates of sustained virological response (SVR) and significantly shortened treatment durations.[15] According to recent publications, SVR rates can reach >95% in patients with compensated CHC and about 80% to 90% patients with decompensated CHC (Child–Pugh B or C).[16–18] However, DAA agents remain to be prescribed mainly for CHC infection. Various studies are already published or underway to assess the use of IFN-free DAA combinations in the treatment of AHC virus monoinfection or coinfection with human immunodeficiency virus (HIV).[19–24] However, evidence and recommendations for AHC virus infection is still limited, especially for those whose disease is complicated with hepatic decompensation. Below, we report the case of a patient with GT1b AHC complicated with overt hepatic decompensation, who was successfully treated with SOF and daclatasvir (DCV) plus ribavirin (RBV).

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2. CASE REPORT

A 76-year-old man with a history of gouty arthritis presented with general malaise for one month. Initially, he felt fatigue and poor appetite for about four weeks followed by yellowish skin and sclerae alongside tea-colored urine for a few days. He had neither fever, change of bowel habit nor abdominal pain after the onset of symptoms. He was admitted to Landseed Hospital, Taoyuan, Taiwan, ROC in September 2017, and there his serum ALT level revealed 1360 U/L (≤40 U/L); aspartate aminotransferase (AST), 725 U/L (≤40 U/L); total bilirubin (T-bil), 4.0 mg/dL (≤1.6 mg/dL); direct bilirubin (D-bil), 3.1 mg/dL (≤0.45 mg/dL). Abdominal sonography showed no structural abnormalities. Five days after admission, serum ALT and AST levels decreased gradually but his T-bil level deteriorated from 4.0 mg/dL to 8.0 mg/dL. Laboratory tests for acute viral hepatitis including serum anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV showed negative results. Because of progressive elevation of T-bil levels, he was transferred to our hospital for further evaluation and management. Upon his arrival at our hospital, physical examination showed yellowish discoloration of skin and sclerae, no palmer erythema or spider angioma, mild tenderness at right upper quadrant abdomen when deep palpation was performed, and no shifting dullness or fluid thrill. Results of his liver function tests were as follows: ALT, 278 U/L; AST, 130 U/L; T-bil, 10.4 mg/dL; D-bil, 8.1 mg/dL; alkaline phosphatase (Alk-p), 188 U/L (≤100 U/L); gamma glutamyl transpeptidase (GGT), 195 U/L (≤60 U/L); albumin, 2.9 g/dL (≥3.6 g/dL); creatinine, 1.1 mg/dL (<1.4 mg/dL); prothrombin time (PT), 10.9 seconds (<11 seconds); and platelet count, 201 × 10^9/L (150-400 × 10^9/L). His calculated model for end-stage liver disease (MELD) score was 17 points. Interestingly, the anti-HCV antibody result at our hospital was positive (ie, anti-HCV seroconversion), which was detected by commercially available assay at these two hospitals (anti-HCV; Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois, USA). The subsequent quantitative HCV RNA result by real-time PCR (Cobas Taqman HCV Test v2.0, Roche Diagnostics) was 3.51 × 10^7 IU/mL (GT1b). Dynamic computed tomography of the liver revealed periportal edema and thickening of the gallbladder wall without space-occupying lesion in the liver or pancreas and also disclosed no biliary tract dilatation. The patient was treated with human serum albumin, glycyrrhizin, and other medications to relieve symptoms. However, the patient had deteriorated fatigue and jaundice after 6 days from hospitalization. Laboratory data were as follows: ALT, 214 U/L; AST, 122 U/L; Alk-p, 167 U/L; GGT, 170 U/L; albumin, 4.2 g/dL; creatinine, 1.30 mg/dL; PT, 10.6 seconds. Besides, conjugated hyperbilirubinemia progressed (T-bil raised up to 20.3 mg/dL; D-bil, 15.2 mg/dL) and calculated MELD score climbed up to 21 points. We also performed antinuclear antibody, antismooth muscle antibody, and antimitochondria antibody tests, which all showed negative results alongside immunoglobulin G (IgG) including IgG4 and serum ceruloplasmin level that revealed within normal ranges. Under the impression of AHC with liver failure, we decided to treat the patient with DAAs after ruling out other possible causes of acute hepatitis. So, we started a combination therapy of Sovaldi (SOF) 400 mg daily and Daklinza (DCV) 60 mg daily plus a low dose of Robatrol (RBV) of 600 mg/day for 12 weeks after explanation and discussion with the patient and his family. After treatment, the HCV RNA levels and laboratory profiles evolved as depicted in Figs. 1 and 2. Obvious declines in T-bil and ALT levels were noted after administration of DAAs and the patient's fatigue and malaise gradually resolved. By week 8, ALT returned to a normal limit (39 U/L) and T-bil returned to normal (0.82 mg/dL) in week 12 (Fig. 2). During week 1, the HCV RNA viral load decreased to 2.12 × 10^5 IU/mL; in week 2 it decreased to 2095 IU/mL; and in week 4 it further decreased to70 IU/mL. In weeks 8, 12, and 24 (post-treatment week 12), the HCV viral load was undetectable (<15 IU/mL) and SVR12 was impressed (Fig. 1).

3. DISCUSSION

GT1 of HCV is the most common genotype at worldwide and subgenotype 1b is most predominant in Europe and Eastern Asia as well as in Taiwan.[9,10] Infection with HCV is usually asymptomatic (50% to 90% of cases), with only a minority of patients presenting with symptomatic AHC, while fulminant liver failure is rare. According to a study of 1053 patients with AHC, the case-fatality rate was reported as 5/1000[25] and the clinical event occurs more frequently in the cases of HCV superinfection among HBV carriers.[26,27] For this patient, no history of underlying liver disease could be traced and the reasons responsible for his fulminant course except old age remains to be clarified.

HCV infection is predominantly transmitted by exposure to blood or body fluids. The patient had not received any blood transfusion during his life and he also denied ingesting herbal medicine or over-the-counter drugs. He had visited two local clinics for one time each near his residence in the countryside of

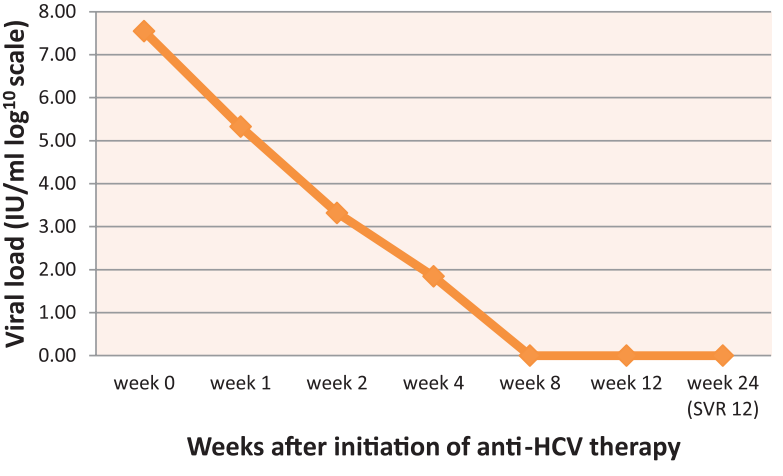

Fig. 1 The HCV viral load subsequently decreased after treatment with sofosbuvir and daclatasvir plus ribavirin. At the beginning of treatment, HCV RNA viral load was 3.51 × 10^7 IU/mL. During week 1, the HCV RNA viral load decreased to 2.12 × 10^5 IU/mL; in week 2, it decreased to 2095 IU/mL; and in week 4, it decreased further to 70 IU/mL. In weeks 8, 12, and 24 (post-treatment week 12), the HCV viral load was undetectable. HCV, hepatitis C virus.

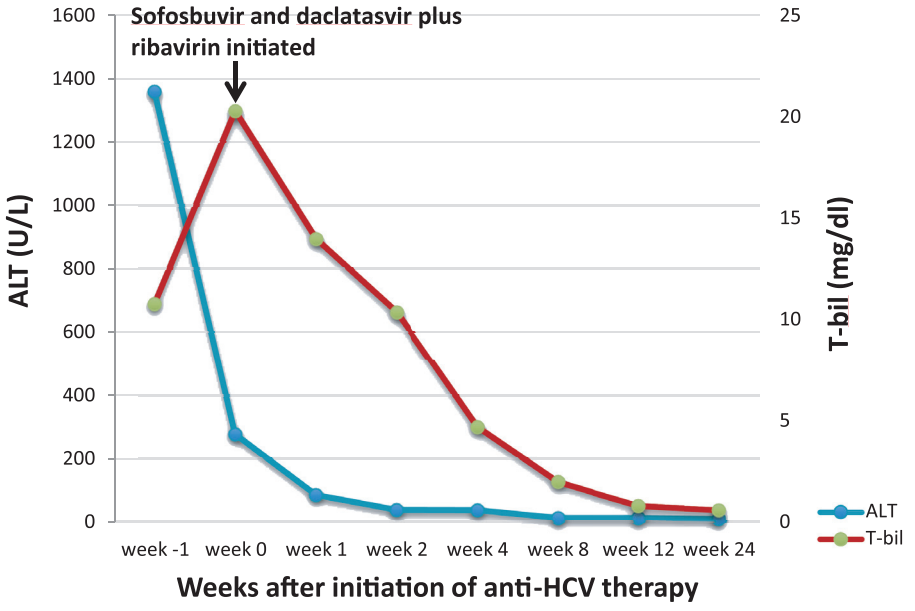

Fig. 2 Liver function gradually recovered after treatment. By week 8, ALT and T-bil returned to baseline levels. ALT, alanine aminotransferase; HCV, hepatitis C virus; T-bil, total bilirubin.

northern Taiwan, where he received intravenous drugs and fluid infusions to relieve his common cold symptoms during July and August 2017. No other possible routes of infection were found. Given the time window of anti-HCV seroconversion, therefore, we thought that AHC may have been transmitted through recent nonsterile needle injection.

At the time of admission to our hospital, the patient presented with deteriorated direct-type predominant hyperbilirubinemia. Antiviral therapy was strongly indicated due to significant hepatic decompensation accompanied with a very high HCV RNA load. IFN-based or protease inhibitor containing all oral DAAs regimens should not be chosen due to evidence of liver failure. Therefore, we selected SOF, a nucleotide NA5B polymerase inhibitor, and DCV, a NS5A inhibitor, as treatment regimen plus RBV 600 mg/day as therapeutic regimen in accordance with his genotype results. After all oral DAAs therapy, patient's subjective symptoms and liver function began to improve. Viral kinetics showed a significant decline of HCV RNA and a more than 2 $\log^{10}$ IU/mL reduction of RNA level was observed after one week of therapy. The HCV RNA level was 70 IU/mL in week 4 and became undetectable (<15 IU/mL) by week 8 and remained so thereafter. During the treatment period, the patient responded well to the therapy and he had no obvious symptoms or abnormal laboratory results that may have been due to DAA or RBV-related adverse events. After completion of 12 weeks of all oral DAAs and post-treatment follow up, he achieved biochemical normalization and SVR12.

Currently, evidence regarding IFN-free DAAs therapy for AHC is still limited and mainly derived from HIV-infected individuals. According to literature reports, rates of SVR12 for compensated AHC range from 21% to 60% with 6 weeks of SOF and RBV, may reach 53% to 92% by 12 weeks of SOF and RBV.[20–22] Rates of SVR12 ranges from 93% after 4 weeks of therapy with SOF plus ledipasvir up to 77% to 100% with 6 weeks therapy of SOF plus ledipasvir.[23,24] Therefore, the European Association for the Study of the Liver (EASL) recommends a combination of SOF and an NS5A inhibitor such as ledipasvir, DCV, or velpatasvir for 8 weeks for AHC-infected patients, which may be prolonged to 12 weeks for patients with AHC and HIV coinfection and/or a baseline HCV RNA level >1 million IU/mL (6.0 $\log^{10}$ IU/mL).[28] The American Association for the Study of Liver Diseases (AASLD) recommends the same type and duration of DAA therapy for CHC as AHC infection.[15]

To date, this is the first case report using SOF and DCV plus a low dose of RBV for 12 weeks for monoinfected AHC with significant hepatic decompensation and extremely high HCV RNA level (3.51×10^7 IU/mL). The RBV dose was adjusted to 600 mg/day as the patient had decreased creatinine clearance (52.3 mL/min). The patient responded well to our treatment and no obvious adverse effects were reported during or after the antiviral therapy. As optimal treatment guidelines including treatment duration and DAA combinations in AHC patients are not well established yet, more studies focusing on IFN-free DAA combinations for AHC patients with or without HIV infection remain necessary to address these important issues.

REFERENCES

1. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol* 2014;**61**(1 Suppl):S45–57.
2. Kao JH. Hepatitis C virus infection in Taiwan: past, present, and future. *J Formos Med Assoc* 2016;**115**:65–6.
3. Liu CH, Kao JH. Nanomedicines in the treatment of hepatitis C virus infection in Asian patients: optimizing use of peginterferon alfa. *Int J Nanomedicine* 2014;**9**:2051–67.
4. 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.
5. Gravitz L. Introduction: a smouldering public-health crisis. *Nature* 2011;**474**:S2–4.
6. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* 2006;**45**:529–38.
7. Loomba R, Rivera MM, McBurney R, Park Y, Haynes-Williams V, Rehermann B, et al. The natural history of acute hepatitis C: clinical presentation, laboratory findings and treatment outcomes. *Aliment Pharmacol Ther* 2011;**33**:559–65.
8. Ward JW. The hidden epidemic of hepatitis C virus infection in the United States: occult transmission and burden of disease. *Top Antivir Med* 2013;**21**:15–9.

9. Nguyen LH, Nguyen MH. Systematic review: Asian patients with chronic hepatitis C infection. *Aliment Pharmacol Ther* 2013;**37**:921–36.
10. Sievert W, Altraif I, Razavi HA, Abdo A, Ahmed EA, Alomair A, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. *Liver Int* 2011;**31**(Suppl 2):61–80.
11. Davis GL, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the united states. *Liver Transpl* 2003;**9**:331–8.
12. van de Laar TJ, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. *Aids*2010;**24**:1799–812.
13. Kanda T, Yokosuka O, Imazeki F, Saisho H. Acute hepatitis C virus infection, 1986-2001: a rare cause of fulminant hepatitis in Chiba, Japan. *Hepatogastroenterology* 2004;**51**:556–8.
14. Thimme R, Oldach D, Chang KM, Steiger C, Ray SC, Chisari FV. Determinants of viral clearance and persistence during acute hepatitis C virus infection. *J Exp Med* 2001;**194**:1395–406.
15. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015;**62**:932–54.
16. Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al.; ASTRAL-4 Investigators. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med* 2015;**373**:2618–28.
17. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr, et al.; SOLAR-1 Investigators. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology* 2015;**149**:649–59.
18. Saxena V, Nyberg L, Pauly M, Dasgupta A, Nyberg A, Piasecki B, et al. Safety and efficacy of simeprevir/sofosbuvir in hepatitis C-infected patients with compensated and decompensated cirrhosis. *Hepatology* 2015;**62**:715–25.
19. Lampejo T, Agarwal K, Carey I. Interferon-free direct-acting antiviral therapy for acute hepatitis C virus infection in HIV-infected individuals: A literature review. *Dig Liver Dis* 2018;**50**:113–23.
20. Naggie S, Marks KM, Hughes M, Fierer DS, Macbrayne C, Kim A, et al.; AIDS Clinical Trials Group (ACTG) A5327 Study Team. Sofosbuvir plus ribavirin without interferon for treatment of acute hepatitis C virus infection in HIV-1-infected individuals: SWIFT-C. *Clin Infect Dis* 2017;**64**:1035–42.
21. El Sayed A, Barbati ZR, Turner SS, Foster AL, Morey T, Dieterich DT, et al.; New York Acute Hepatitis C Surveillance Network. Sofosbuvir in the treatment of early HCV infection in HIV-infected men. *HIV Clin Trials* 2017;**18**:60–6.
22. Martinello M, Gane E, Hellard M, Sasadeusz J, Shaw D, Petoumenos K, et al. Sofosbuvir and ribavirin for 6 weeks is not effective among people with recent hepatitis C virus infection: the DARE-C II study. *Hepatology* 2016;**64**:1911–21.
23. Rockstroh JK, Bhagani S, Hyland RH, Yun C, Dvory-Sobol H, Zheng W, et al. Ledipasvir-sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. *Lancet Gastroenterol Hepatol* 2017;**2**:347–53.
24. Deterding K, Spinner CD, Schott E, Welzel TM, Gerken G, Klinker H, et al.; HepNet Acute HCV IV Study Group. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (hepnet acute HCV IV): an open-label, single-arm, phase 2 study. *Lancet Infect Dis* 2017;**17**:215–22.
25. Spada E, Mele A, Mariano A, Zuccaro O, Tosti ME; SEIEVA collaborating group. Risk factors for and incidence of acute hepatitis C after the achievement of blood supply safety in Italy: results from the national surveillance system. *J Med Virol* 2013;**85**:433–40.
26. Liaw YF, Chen YC, Sheen IS, Chien RN, Yeh CT, Chu CM. Impact of acute hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. *Gastroenterology* 2004;**126**:1024–9.
27. Sagnelli E, Coppola N, Marrocco C, Onofrio M, Sagnelli C, Coviello G, et al. Hepatitis C virus superinfection in hepatitis B virus chronic carriers: a reciprocal viral interaction and a variable clinical course. *J Clin Virol* 2006;**35**:317–20.
28. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol* 2017;**66**:153–94.