Published in final edited form as:

Hepatol Int. 2016 July ; 10(4): 616–623. doi:10.1007/s12072-016-9719-4.

Examining the clinical course of genotype 1 chronic hepatitis C patients treated with the cosmos regimen: including patients with advanced liver disease and East Asian ancestry

Marina Roytman^{1,2}, Resham Ramkissoon^{2,3}, Christina Wu², Leena Hong¹, Ruby Trujillo¹, Leslie Huddleston¹, Peter Poerzgen¹, Todd Seto¹, Linda Wong¹, and Naoky Tsai^{1,2}

Resham Ramkissoon: resham@hawaii.edu

¹Liver Center, Queen's Medical Center, Honolulu, HI, USA

²Department of Medicine, John A. Burns School of Medicine, Honolulu, HI, USA

³550 S Beretania Street, Suite 405, Honolulu, HI 96813, USA

Abstract

Background/objectives—The COSMOS study was a phase 2a clinical trial that showed high cure rates of genotype 1 chronic hepatitis C (CHC) and a favorable side effect profile using a 12-week regimen of simeprevir + sofosbuvir (SIM + SOF). Given the small number of patients treated with the SIM + SOF regimen in the COSMOS trial, there is uncertainty regarding the efficacy and safety of this combination therapy. We now report our experience with the COSMOS regimen in the multiethnic population of Hawaii, including patients of East Asian ancestry and with decompensated cirrhosis.

Methods—This study is a retrospective review of 138 patients treated with a fixed dose regimen of SIM 150 mg and SOF 400 mg daily at a single referral center. We collected data on demographics, side effects, laboratory studies and sustained virological response (SVR). Statistical analysis was performed with Stata v8.2 software.

Results—Baseline characteristics of the 138 patients initiated with SIM + SOF therapy were: 68.8 % cirrhotic (22.1 % of those Child-Pugh Class B), 37 % Asian, 11.6 % Pacific Islander, 63 % male, mean age 61.3 ± 7.8 years, mean BMI 27.8 ± 6.1 kg/m², 26.8 % diabetic, 63.8 % genotype 1a, 44.9 % previously treatment experienced. A total of 100 % of patients that completed therapy

Compliance with ethical standards

Conflict of interest Naoky Tsai has received research grants, unrelated to this research project, from the following companies; AbbVie, Janssen, Gilead Sciences, BMS and Beckman Coulter. Naoky Tsai is on the advisory board of Gilead Sciences and AbbVie. Naoky Tsai is part of the speaker's bureau for AbbVie, Janssen, Gilead Sciences, BMS, Salix and Bayer Healthcare. Marina Roytman is on the speaker's bureau and advisory board for Gilead and Sciences. Linda Wong is on the speaker's bureau for Gilead Sciences. All other authors have no conflicts of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Queen's Medical Center Research and Institutional Review Committee (approval #RA-2014-048) as well as with the 1964 Helsinki Declaration and its later amendments. This article does not contain any studies with animals performed by any of the authors.

Informed consent A waiver for informed consent was obtained by the Queens Medical Center Institutional Review Committee (approval #RA-2014-048). This study fulfilled the following criteria: (1) an observational study that involved no more than minimal risk to subjects, (2) a waiver of informed consent did not adversely affect subjects' right and welfare, (3) the research could not practicably be conducted without the waiver, and (4) the patient received all pertinent information during office visits as they are followed at the Queen's Liver Center.

($n = 137$) had undetectable viral loads at end of treatment (EOT). Twelve patients relapsed post-treatment resulting in an overall 12 week SVR (SVR12) rate of 89.1 %. 95 % of decompensated cirrhotic patients achieved SVR12, compared to 85.3 % of compensated cirrhotic patients and 93 % of non-cirrhotic patients. 92 % of Asian patients achieved SVR12 compared to 87.5 % in non-Asian patients. There were no statistically significant differences in SVR12 between treatment naive and treatment experienced patients (86.8 vs 91.9 %). 87.5 % of post-transplant patients achieved SVR12. The main side effects were headache 16.2 %, fatigue 24.2 %, pruritis 14.1 %; none were >grade 2 in severity. There were no differences in side effect profiles of patients with decompensated cirrhosis. Pruritis only was statistically significant between Asians and non-Asians (22 vs 5.7 %). Trends toward improvement in platelet counts and total bilirubin were noted at 12-weeks post treatment, while improvement in albumin in cirrhotic patients reached statistical significance (3.77–4.01 mg/dL, $p = 0.0108$).

Conclusions—The 12-week fixed dose course of SIM + SOF was well tolerated in a multiethnic population of primarily cirrhotic patients, including those with decompensated disease. This real world trial achieved SVR12 rates comparable to the COSMOS data. Higher incidence of adverse side effects was not observed with an exception of higher rate of pruritis in Asians. The increase in albumin in cirrhotic patients was statistically significant and suggested early improvement in synthetic function following viral eradication. Higher BMI ($> 30 \text{ kg/m}^2$) was the only factor that correlated with post-treatment relapse by multivariate analysis.

Keywords

Hepatitis C; Treatment; Decompensated cirrhosis; East-Asian; Simeprevir + sofosbuvir

Introduction

The hepatitis C virus (HCV) is the most common, chronic blood-borne infection in the United States. HCV infection is the leading cause of liver transplantation, liver neoplasia and one of the leading causes of cancer-related deaths in the US [1]. Chronic HCV is associated with a very high morbidity and mortality; 20 % of chronically infected patients develop cirrhosis within 25 years and 25 % of those patients will go on to develop decompensated cirrhosis and hepatocellular carcinoma. Vertical transmission of HCV occurs in approximately 5.8 % of pregnant women who are human immunodeficiency virus (HIV) negative, with the approximate doubling of the HCV transmission rate in HIV positive pregnant women to 11.5 % [2]. Worldwide, the number of chronic HCV infections exceeds 200 million. The CDC approximates that 3.2 million of these cases are in the US alone [3, 4].

In January 2014, the AASLD treatment guidelines for interferon (IFN)-ineligible patients infected with genotype 1 HCV were changed to include a combination of simeprevir + sofosbuvir (SIM + SOF) and subsequently approved for use by the FDA at the end of the year. Simeprevir is a potent, oral HCV NS3/4A protease inhibitor and sofosbuvir is a HCV nucleotide NS5B polymerase inhibitor. The changes to the AASLD guidelines were based on the 2014 COSMOS clinical trial, a phase IIa clinical trial using SIM + SOF ± Ribavirin (RBV) that yielded 92.9 % SVR12. The addition of RBV to SIM + SOF dual-therapy did not improve SVR rates. Furthermore, side effects were milder in patients treated with SIM +

SOF alone compared to those who had RBV included in their treatment regimen [5]. The previous triple therapy of PEG-IFN, RBV and either telaprevir or boceprevir posed difficulties with PEG-IFN intolerance, difficulties with administration and adherence issues due to the length of the regimen, adverse effects, and resulted in inferior cure rates [2]. In the COSMOS trial, only 28 patients were treated with SIM + SOF alone, 14 with METAVIR scores F0–F2 and 14 with METAVIR scores F3–F4. This study focuses on the 12-week regimens of SIM + SOF alone in patients who are either treatment naive, treatment experienced, have varying degrees of fibrosis and are of a broad range of ethnicities.

Notably, patients of East-Asian ancestry and patients with more advanced liver disease have higher serum concentrations of SIM than patients of non-East Asian ethnicities and patients without advanced liver disease [6]. By assessing a larger cohort of East-Asian patients and patients with advanced liver disease the aim of this study is to be able to accurately predict and understand adverse effects experienced by these types of patients, as well as to evaluate treatment outcomes in this patient cohort treated with the SIM + SOF regimen.

Methods

Study design and patient population

This is a retrospective study of genotype 1 HCV RNA positive patients at a single referral center. Patients were started on a 12-week regimen of SIM + SOF once a day at the Queen's Liver Center between January 2014 and March 2015. All patients were treated with a standard regimen of SIM 150 mg and SOF 400 mg.

The following baseline data were collected: age, gender, BMI, prior treatment experience, presence of cirrhosis and comorbidities. Baseline laboratory values were defined as the value on or closest to the patient's treatment start date which included alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, serum creatinine, international normalized ratio (INR), hemoglobin, hematocrit, platelet count, absolute neutrophil count, HCV RNA and genotype. Cirrhosis was defined by clinical parameters, namely, evidence of decompensated disease, imaging and laboratory values. Degree of cirrhosis was defined using the Child-Turcotte-Pugh (CTP) classification of cirrhosis severity; decompensated cirrhosis was defined as CTP class B.

The Queen's Liver Center providers chose to treat the patients with SIM + SOF regimen according to AASLD guidelines primarily due to criteria of IFN intolerance or ineligibility. These criteria included presence of cirrhosis, liver transplant, renal disease, depression, autoimmune condition, prior IFN intolerance, hematological disorder, platelets <100,000/mL, and albumin <3.5 mg/dL. All data were collected retrospectively.

Treatment outcomes

SVR was evaluated using HCV RNA results available at 4 and 12 weeks after the end of treatment (EOT), herein referred to as SVR4 and SVR12, respectively. HCV RNA was documented as detectable or undetectable based on reported HCV RNA results (<15 IU/mL). Patients were considered to have a virological cure if they achieved SVR12. While SVR24 has been considered the standard for establishing SVR and virological cure in

treated patients, previous literature has reported a strong correlation between SVR24 and SVR12 with a positive and negative predictive value greater than 98 % [7–9].

Adverse events

Adverse events (AE) were monitored throughout follow-up at the Queen's Liver Center during the 12 weeks of treatment and during the post-treatment period for any residual effects. The AEs that were monitored were those that were frequently seen in the COSMOS study, which includes headache, fatigue, nausea, rash/photosensitivity, pruritis and myalgia. They were classified from grade 1 to grade 5. Grade 1 AE included asymptomatic or mild symptoms, clinical or diagnostic observations only, and no intervention indicated. Grade 2 AE included moderate, minimal, local or noninvasive intervention indicated, and limiting age-appropriate instrumental activities of daily living (ADL). Grade 3 AE included severe or medically significant but not immediately life threatening, hospitalization or prolongation of hospitalization indicated, disabling, and limiting self care ADL. Grade 4 AE included life-threatening, urgent intervention indicated. Grade 5 AE included deaths related to an AE.

Data collection and statistical analysis

Care-Link/EPIC Electronic Medical Record (EMR) was used for data collection. The data were collected in a Microsoft Excel Spreadsheet which included the patients' age, gender, BMI, HCV genotype, past medical history, history of prior treatment for HCV, SIM + SOF regimen start date, baseline HCV RNA viral load, HCV RNA viral load throughout treatment and adverse events related to SIM + SOF treatment. Patients were identified by a randomly assigned patient ID number and otherwise completely de-identified according to the criteria outlined by the Clinical Research and HIPAA Privacy Rule. Results were analyzed by the intention-to-treat (ITT) approach using Stata v8.2 software. Continuous variables were summarized by descriptive statistics (mean, median, range, standard deviation). Statistical tests were two sided and the *p* value level was set at 0.05. This statistical analysis was used to determine *p* values and odds ratios with 95 % confidence intervals.

Results

Baseline characteristics

A total of 138 genotype 1a or 1B HCV-RNA positive patients were treated with a combination SIM + SOF, once a day for 12 weeks. Table 1 describes the baseline characteristics of the patient cohort. Baseline demographics showed 63 % male gender, an average age of 61.3 ± 7.8 years and BMI of 27.8 ± 6.1 kg/m². The most common ethnicity in our cohort was Caucasian (46.4 %) and patients of Asian ethnicity represented 36.2 % of the patient cohort. This study included 68 % (*n* = 95) cirrhotic patients, 22.1 % (*n* = 20) of which were decompensated (all CTP class B). Patients with genotype 1a HCV comprised 63.8 % of our patient cohort. The most common comorbidities were hypertension (42 %), diabetes mellitus (26.8 %) and depression (18.1 %).

Virological outcomes

The chronology of our patient cohort treated with SIM + SOF is outlined in Fig. 1. Of the 138 patients that were initiated with SIM + SOF treatment, 137 completed the entire 12 weeks of therapy and one patient discontinued treatment due to rash and pruritis. This particular patient was Caucasian and non-cirrhotic. Viral load was undetectable in 100 % of patients that reached EOT. At 4 weeks post-treatment, 126/137 patients achieved SVR4. However, nine patients were found to have a detectable HCV viral load, one patient died from a variceal hemorrhage and one was lost to follow up. At 12 weeks post-treatment, three additional patients were found to have a detectable HCV viral load, totaling 12, with 123/126 patients achieving SVR12 (Fig. 1).

Based on an ITT analysis, the overall SVR12 of this study was 89.1 %. There was a 96.8 % concordance rate between SVR4 and SVR12. The SVR12 rates for patients without cirrhosis, cirrhosis and decompensated cirrhosis (CPT class B) were 93.0, 85.3 and 95 %, respectively. There were no statistically significant differences in SVR12 rates observed between these subgroups of patients (Fig. 2). Cirrhotic and non-cirrhotic patients did not differ in their SVR rates with statistical significance (OR 2.2632, 95 % CI 0.4754–10.774, $p = 0.3049$). There were seven post-transplant patients in our cohort, one patient relapsed following treatment resulting in SVR12 of 87.5 %. Comparing the difference in SVR between ethnicities, 92 % of patients of Asian ancestry achieved SVR12, compared with 87.5 % of non-Asian patients (Fig. 3). These differences did not reach statistical significance.

The effect of treatment experience on SVR was also evaluated. Treatment naïve patients achieved an SVR12 of 86.8 %. In this group of treatment naïve patients, 85.2 % of cirrhotic patients achieved SVR12 compared to 90.9 % of non-cirrhotic patients. In treatment experienced patients, 91.9 % achieved SVR12. In this group of treatment experienced patients, 90.2 % of cirrhotic patients achieved SVR12 and 94.7 % of non-cirrhotic patients achieved SVR12 (Fig. 3). Treatment experience had no statistically significant impact on SVR.

Relapsed patients

There were 12 patients that relapsed following 12 weeks of therapy with SIM + SOF. Patients with a BMI ≥ 30 kg/m² were independently associated with relapse following treatment after controlling for age, cirrhosis, and prior treatment in a multivariate analysis (OR 7.90, 95 % CI 2.03–30.7, $p = 0.0029$). Additionally, males were more common in this cohort ($n = 10$) but were not independently associated with relapse (OR 3.18, 95 % CI 0.67–15.1, $p = 0.2099$). Genotype 1a versus 1b was also not independently associated with relapse (OR 2.84, 95 % CI 0.60–13.5, $p = 0.1888$). Lastly, 10/12 patients were found to be cirrhotic (Table 2).

Effect on Liver Function and Regimen Safety

After 12 weeks post-therapy, several improvements were noted with regards to liver function. Albumin levels in cirrhotic patients increased from 3.77 to 4.01 mg/dL, which was statistically significant ($p = 0.0108$). Although not statistically significant, the following

trends were observed: total bilirubin decreased from 1.10 to 0.897 mg/dL and platelet count improved from 138×10^3 to $146 \times 10^3/\text{mL}$. The incidence of pruritis was found to be 22.0 % in patients of East Asian ancestry compared to 5.7 % of non-East Asian patients ($p = 0.0171$) as shown in Fig. 4. The AST-to-platelet ratio index (APRI) was calculated for patients before and after treatment based on available data. Out of 76 cirrhotic patients, 66 were found to have an APRI >0.7 prior to treatment. Out of these patients, 62/66 saw a decrease in APRI by SVR12 and 52/66 achieved an APRI of <0.7 . Out of 31 non-cirrhotic patients, 21 patients had an APRI >0.7 at baseline. Out of these 21 patients, 17 had an APRI <0.7 by SVR12. Lastly, the MELD score was calculated for 56 patients (based on available data) and all patients had a MELD score of <19 prior to treatment. There were 23 patients that had a decrease in their MELD score post-treatment, with an average decrease of 1.49 (standard deviation of 1.07).

Discussion

Effectiveness versus efficacy of SIM + SOF

This study was done to evaluate the effectiveness of the SIM + SOF combination therapy in a large, multiethnic cohort of primarily cirrhotic patients. We want to highlight the importance of distinguishing efficacy, the outcomes from clinical trials and effectiveness, as well as the outcomes in routine practice settings [6]. COSMOS reported SVR12 of 92.9 % which is comparable to the SVR12 of 89.1 % in our study. The effectiveness of a therapy in a real-life setting is expected to be slightly lower than efficacy because clinical trials have stringent inclusion criteria and close monitoring that may not accurately reflect the real-world patient population with CHC. Despite including close to 70 % of cirrhotic patients in our study with a significant proportion of patients with decompensated disease, SVR12 rates are comparable to the COSMOS results with a favorable side effect profile indicating effectiveness and safety of the SIM + SOF regimen in a real-life clinical setting.

Although not quite statistically significant, the highest SVR rates were in patients with decompensated cirrhosis (95 %, 19/20). The single decompensated patient who did not achieve SVR12 died from a variceal hemorrhage at week 5 post-treatment. Esophagogastroduodenoscopy showed grade 2 varices 5 months prior to starting SIM + SOF therapy, and FibroScan score was 53.2 kPa, indicative of very significant portal hypertension. All patients with decompensated cirrhosis (100 %, 20/20), including the patient who died of a variceal hemorrhage, achieved SVR4. While it is premature to draw definitive conclusions about the use of SIM + SOF therapy in this challenging group of patients, we can find reassurance in the fact that treatment was well tolerated and achieved high cure rates compared to the patients with a more preserved liver function. A larger sample size will be necessary to determine if decompensated cirrhotics truly have a better response rate and validate this unexpected trend demonstrated in the current study.

Our study included 37 % patients of East-Asian ancestry. A non-statistically significant increase in SVR rates was noted in Asian patients compared to their non-Asian counterparts. This difference may be attributed to the higher serum concentrations of SIM noted in East-Asian patients in previous clinical trials [10]. With increased serum concentrations of SIM, an increased incidence of side effects is expected. There was a statistically significant

difference between the incidence of pruritus in Asian patients (22.0 %) compared to non-Asian patients (5.7 %, $p = 0.0171$), however no other differences in side effects reached statistical significance. Larger studies are needed to further evaluate the potential impact of higher SIM concentrations on cure rates and side effect profile in East Asian populations.

Possible predictors of treatment failure

Common characteristics of relapsed patients included male gender (10/12), genotype 1a chronic hepatitis C (10/12) and compensated cirrhosis (10/12). After controlling for age, cirrhosis and prior treatment in a multivariate analysis, only a higher BMI ($> 30 \text{ kg/m}^2$) was independently associated with relapse (OR 7.90, 95 % CI 2.03–30.7, $p = 0.0029$). Therefore, out of all the characteristics described in Table 2, higher BMI ($> 30 \text{ kg/m}^2$) was the strongest predictor of relapse in the post-treatment follow-up period for patients in our study. In clinical trials, the presence of the Q80K was associated with lower SVR in genotype 1a patients treated with SIM + IFN + RBV triple therapy, indicating that the Q80K polymorphism may be a risk factor for relapse [11]. None of the patients in our study that relapsed were Q80K positive, however, not all patients were tested. Further investigation could yield results indicating that sofosbuvir may overcome the treatment hurdle of the Q80K polymorphism in patients treated with simeprevir. We believe such an investigation is warranted, given the importance of this mutation in predicting treatment failure.

Effect on liver function

Albumin, total bilirubin and platelet counts improved at 12 weeks post-treatment in patients with cirrhosis compared to baseline values. The statistically significant improvement in serum albumin, from baseline to 12-week post treatment, suggests improvements in hepatic synthetic function with eradication of the virus. Longer time after achieving virological cure may be required to demonstrate statistically significant improvement in platelets which can be considered a surrogate marker for improving portal hypertension. A considerable number of cirrhotic and non-cirrhotic patients who had an APRI > 0.7 saw a decrease in APRI index to < 0.7 . There was no statistically significant difference in APRI changes between cirrhotic and non-cirrhotic patients. According to a meta-analysis of 40 studies, an APRI score of > 0.7 had a 77 % sensitivity and 72 % specificity for hepatitis C related fibrosis [12]. However, only very limited experience exists with APRI index in relationship to improving fibrosis. Long-term follow-up with vibration controlled transient elastography or liver biopsy is needed to establish usefulness of APRI index for documentation of fibrosis improvement. Finally, MELD scores were calculated before and after treatment to assess mortality risk of patients in our treatment group. There was no significant improvement in 3-month mortality after SIM + SOF therapy; MELD scores only improved by an average of 1.49 (standard deviation of 1.07) post-treatment.

Limitations

There are some limitations to our study. First, this study is retrospective in nature, therefore certain factors that may potentially be predictive of response to therapy, such as Q80K or IL28B, are lacking in all patients. Second, patient ethnicity was self-reported and does not adequately reflect patients with mixed ethnicities which may affect observed differences between Asian and non-Asian patients. Third, all of the patients with decompensated disease

who were CPT class B, results may not be applicable to patients with more advanced disease.

Conclusions

The SIM + SOF regimen in a real life setting of a multi-ethnic cohort of patients, including patients with decompensated cirrhosis, yielded an overall SVR12 of 89.1 % which is comparable to COSMOS data. No clinical increase in adverse events was noted in patients with advanced liver disease or in patients with East Asian ancestry. Statistically significant improvement in albumin and a trend toward improvement in platelets may suggest improved hepatic fibrosis and potentially long-term reduction in portal hypertension. Ultimately, longer follow-up in a larger cohort will be required to confirm the interesting trends observed in this study.

Acknowledgments

The findings, conclusions, etc., of this study do not necessarily reflect the views of The Queen's Medical Center.

Funding: None.

Abbreviations

HCV	Hepatitis C virus
CHC	Chronic hepatitis C
AASLD	American Association for the Study of Liver Diseases
SIM	Simeprevir
SOF	Sofosbuvir
IFN	Interferon
RBV	Ribavirin
CTP	Child-Turcotte-Pugh
EOT	End of treatment
SVR	Sustained virological response
AE	Adverse event
EMR	Electronic medical record

References

1. Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in the USA: an estimate of true prevalence. *Liver Int.* 2011; 31:1090–1101. [PubMed: 21745274]
2. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis.* 2014; 59:765. [PubMed: 24928290]

3. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med.* 2006; 144:705–14. [PubMed: 16702586]
4. CDC. Viral hepatitis—hepatitis C information. Center of Disease Control and Prevention; division of viral hepatitis; 2015.
5. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study. *The Lancet.* 2014; 384:1756–65.
6. Vo, Kevin P., et al. Poor sustained virological response in a multicenter real-life cohort of chronic hepatitis C patients treated with pegylated interferon and ribavirin plus telaprevir or boceprevir. *Digest Dis.* 2015; 60:1045–51.
7. Chen J, Florian J, Carter W, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. *Gastroenterology.* 2013; 144:1450–55. [PubMed: 23470616]
8. Martinot-Peignoux M, Stern C, Maylin S, et al. Twelve weeks post-treatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. *Hepatology.* 2010; 51:1122–26. [PubMed: 20069649]
9. Medrano J, Barreiro P, Resino S, et al. Rate and timing of hepatitis C virus relapse after a successful course of pegylated interferon plus ribavirin in HIV-infected and HIV-uninfected patients. *Clin Infect Dis.* 2009; 49:1397–1401. [PubMed: 19814621]
10. Medivir, AB. Highlights of Prescribing Information [prescribing information]. Stockholm: 2013. Olysio™ (simeprevir) capsule.
11. Verloes, R., Shishido, A. Phase I safety and PK of TMC435 in healthy volunteers and safety, PK and short-term efficacy in chronic hepatitis C infected individuals. Paper presented at: Japanese Hepatology Congress; 2009; Kobe, Japan. Abstract O-32 4–5
12. Lin ZH, Xin YN, Dong QJ, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology.* 2011; 53:726–36. [PubMed: 21319189]

Fig. 1.

Chronology of 138 patients while on SIM + SOF therapy and during post-treatment follow up. 138 patients were started on SIM + SOF therapy, once a day for 12 weeks. All patients were asked to follow up every 2–4 weeks for clinical evaluation and blood draws checking viral load and other laboratory values. Only a single patient was discontinued from treatment due to an adverse reaction, severe rash and pruritis. Of the 137 of patients that completed 12 weeks of therapy, 100 % had an undetectable viral load. At 4 weeks post treatment, nine patients were found to have a detectable viral load (>15 IU/mL) and considered to have relapse on treatment. One patient deceased in hospital due to an unrelated variceal hemorrhage and one other patient was lost to follow up. The remaining 126 patients achieved SVR4. At 12 weeks post therapy, 123 patients achieved SVR12 and were considered to be virologically cured. However, another three patients relapsed, totaling 12 patients, in the post-treatment follow up period

Fig. 2.

SVR12 rates according to levels of fibrosis and transplant history (intention-to-treat analysis). Analysis of the result for SVR12 was based on an intention-to-treat analysis. Despite having lost patients to follow up and death from complications of their illness, this study yielded an overall SVR12 rate of 89.1 %. There was no statistically significant difference in the SVR rates between cirrhotic and non-cirrhotic patients (OR 2.2632, 95 % CI 0.4754–10.774, $p = 0.3049$). Decompensated and compensated cirrhosis patient were differentiated based on their CTP score; CTP class A were categorized as compensated and CTP class B or C were categorized as decompensated. 95 % of the decompensated cirrhotic patients achieved SVR12 and a virological cure. 85.3 % of compensated cirrhosis patients achieved SVR12. 93.0 % of patients without cirrhosis achieved SVR12. Lastly, there were eight post-transplant patients in this study, seven of which achieved SVR12

Fig. 3.

SVR rates according to prior treatment experience, presence of cirrhosis and ethnicity.

SVR12 rates shown in the figure are treatment-experienced and treatment-naïve patients, further divided into cirrhotic and non-cirrhotic groups. In the treatment naïve group, 90.9 % of non-cirrhotic patients achieved SVR12 and 85.2 % of cirrhosis patients achieved SVR12. Patients who had prior treatment experience, including prior non-responders or relapse to IFN or triple therapy, had higher SVR12 rates than treatment naïve patients. In treatment experienced patients, 94.7 % of non-cirrhotic patients achieved SVR12 and 90.2 % of cirrhotic patients achieved SVR12. The SVR12 rate for all treatment naïve patients was 86.8 % (66/76), whereas 91.9 % (57/62) of patients with prior treatment experience achieved SVR12 (not shown in the figure). Treatment experience had no statistically significant impact on SVR. 92.0 % of patients who reported East-Asian ethnicity achieved SVR12 while 87.5 % of non-East Asian patients achieved SVR12. There was no statistically significant difference in SVR between these two ethnic groups (OR 1.7600, 95 % CI 0.5388–5.7486, $p = 0.3492$)

Fig. 4.

Albumin, total bilirubin, platelet count before and after SIM + SOF therapy in cirrhosis patients. Laboratory values (serum albumin, total bilirubin and platelet count) were measured at baseline, before initiating SIM + SOF therapy, and after 12 weeks of post-treatment follow up. There was a statistically significant increase in serum albumin from 3.77 to 4.01 mg/dL ($p = 0.0108$) and a considerable increase in platelet count from $138 \times 10^3/\text{mL}$ to $146 \times 10^3/\text{mL}$ ($p > 0.05$) following treatment. Total bilirubin decreased from an average of 1.10 to 0.897 mg/dL ($p > 0.05$) following treatment. Neither the improvements in platelet count and total bilirubin were found to be statistically significant. The incidence of adverse events was monitored in patients during treatment and in the post-treatment follow-up period. 22.0 % of Asian patients experienced pruritis and only 5.7 % of non-Asian patients experienced pruritis. This difference was statistically significant ($p = 0.0171$)

Table 1

Demographic data of 138 patients initiated with 12 weeks of SIM + SOF therapy

Characteristics	Total cohort (N = 138)
Age (years)	61.3 ± 7.8
BMI (kg/m ²)	27.8 ± 6.1
Male gender	63.0 % (n = 87)
Asian	37.0 % (n = 51)
Hawaiian/Pacific Islander	11.6 % (n = 16)
Caucasian	46.4 % (n = 64)
African American	5.1 % (n = 7)
Cirrhosis	68.8 % (n = 95)
Decompensated cirrhosis	22.1 % (20/95)
Post liver transplant	5.8 % (n = 8)
BMI > 30 kg/m ²	26.1 % (n = 36)
Diabetes	26.1 % (n = 36)
Coronary artery disease	2.9 % (n = 4)
Prior treatment experience	44.9 % (n = 62)
Genotype 1a	63.8 % (n = 88)
Genotype 1b	36.2 % (n = 50)
IL28B, non-CC	53.2 % (25/47)
Q80K positive	22.2 % (8/36)

Table 2

Characteristics of the 12 patients who relapsed in the post-treatment follow-up period

Patient number	Age (years)	Sex	BMI	Race	Genotype	HCV RNA (IU/cc)	Cirrhosis	Prior Tx	IL28B	Q80K
1	60	M	20.1	Asian	1a	660,846	Yes	No	-	-
2	53	M	31.2	Asian	1a	2,572,707	Yes	Yes	-	-
3	47	M	39.5	Asian	1a	2,623,447	Yes	Yes	-	No
4	64	M	34.9	White	1a	3,964,049	No	No	-	No
5	63	M	30.0	Asian	1b	4,770,345	Yes	Yes	CC	-
6	66	M	21.1	Black	1a	2,828,945	Yes	No	TT	-
7	54	F	41.3	Asian	1a	3,583,174	Yes	No	-	No
8	54	M	38.7	White	1a	1,881,201	Yes	No	-	-
9	70	M	30.6	Black	1a	2,709,776	No	Yes	-	-
10	42	F	42.8	White	1a	372,424	Yes	No	CC	-
11	64	M	33.6	White	1a	2,892,014	Yes	Yes	CT	No
12	50	M	26.6	Asian	1b	812,263	Yes	No	-	-