Journal of Antivirals & Antiretrovirals

Lee SW et al., J Antivir Antiretrovir 2018, 10:3
DOI: 10.4172/1948-5964.1000176

Research Article Open Access

Treatments of Chronic Hepatitis C Genotype 1b with Oral Paritaprevir/Ritonavir/Ombitasvir+Dasabuvir or Daclatasvir/Asunaprevir: A Real-World Data from Taiwan

Shou-Wu Lee[1,2*]

[1]*Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan*

[2]*Department of Internal Medicine, Chung Shan Medical University, Taichung, Taiwan*

[*]**Corresponding author:** Lee SW, Division of Gastroenterology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung 1650 Taiwan Boulevard, Sec. 4, Taichung 40705, Taiwan, Tel: 886-4-23592525; E-mail: ericest@vghtc.gov.tw

Received date: August 21, 2018; **Accepted date:** September 10, 2018; **Published date:** September 20, 2018

Abstract

Background: Hepatitis C Virus (HCV) genotype 1b is predominant in Taiwan. We report here using real-world data on a chronic HCV genotype 1b-infected patient given treatments of oral Pro-D or DAC/ASV.

Methods: Data from subjects with chronic hepatitis C genotype 1b-infection undergoing DAAs therapy was retrospectively collected from October 2015 to January 2017. The DAAs regimens included a 12-week Pro-D and 24-week DCV+ASV. The therapeutic effectiveness and safety, including ALT, bilirubin, EOTVR and SVR at 12 weeks were all recorded.

Results: Among all 81 subjects, 60 and 21 cases belonged to the Pro-D group and DCV/ASV group, with the rate of EOTVR and SVR12 being 98.3% and 90.5% respectively. Elevation of ALT was noted at the third month of DCV/ASV treatment, and increasing bilirubin was found at the secondary weeks of Pro-D treatment.

Conclusion: Our study found SVR12 were 90.5% to 98.3% and 90.5%. Elevated liver function parameters were noted during the therapeutic period.

Keywords: Direct-acting antivirals; Hepatitis C; Viremia

Introduction

Chronic Hepatitis C Virus (HCV) infection is one of the most significant causes of chronic liver disease, cirrhosis, and hepatocellular Carcinoma (HCC) [1]. Six major HCV genotypes have been identified. Genotype 1 is found worldwide, with subtype 1a predominating in the USA, and subtype 1b predominating in East Asia, including Japan, China, Korea, and Taiwan [2]. Current treatment guidelines recommend the use of Interferon (IFN)-free direct-acting antiviral agent (DAA) regimens for the treatment of non-decompensated cirrhotic HCV genotype 1b-infected patients, including elbasvir/grazoprevir, glecaprevir/pibrentasvir, sofosbuvir/ledipasvir and sofosbuvir/velpatasir [3]. Paritaprevir/ritonavir/ombitasvir+Dasabuvir (Pro-D) was classified as an alternative regimen because of potentially prescribing complexity and fluctuation of liver function parameters during its treatment period [3]. In Japan and Taiwan, a combination 24-week therapy with daclatasvir (DCV), a nonstructural protein 5A (NS5A) protease inhibitor, and asunaprevir (ASV), a nonstructural protein 3 (NS3) protease inhibitor, was approved for the treatment of patients with HCV-1b infection [4]. Similarly, the long therapeutic period, less efficacious and alternation of liver function parameters were the worrying issues to this regimen. However, the costs of these regimens were cheaper, and their cost-effectiveness should be estimated. Herein, we report on real-world data regarding a chronic HCV genotype 1b-infected patient with treatment using Pro-D and DCV/ASV.

Methods

Data from subjects experiencing chronic HCV genotype 1b-infection with Pro-D or DCV/ASV, who visited the Medical Screening Center at Taichung Veteran General Hospital, were retrospectively collected from October 2015 to January 2017. The cases were classified as different DAA regimens: Pro-D of a 12-week period, and DCV/ASV of a 24-week period. The general data of enrolled patients, including age, gender, cirrhosis status, and the previous HCC or IFN treatment history of each individual was recorded. The enrollment criteria included [1] seropositivity for anti-HCV longer than 6 months [2]; a completed pan-DAA therapeutic period except in cases with virologic failure to DAAs. The exclusion criteria included [1] a decompensated cirrhosis [2]; previous DAAs treatment [3]; decompensated cirrhosis or HCC without remission [4]; co-infection with the human immunodeficient virus (HIV) or any other identified liver disease, such as autoimmune disease, Wilson's disease or primary biliary cirrhosis.

The serologic data, including HCV RNA (Roohe, Cobas TaqMan48, USA), Alanine aminotransferase (ALT) and bilirubin, were recorded both before and during the therapeutic period. Virologic response (VR) 4 was defined as undetected HCV-RNA at 4 weeks after start of DAAs. End-of-treatment virologic response (EOTVR) was defined as

undetectable HCV RNA at the conclusion of treatment. Sustained virologic response (SVR) 12 was defined as undetectable HCV RNA 12 weeks after therapy had been completed.

Data is expressed as standard deviation of mean for each of the measured parameters. Gender, treatment experience, cirrhosis status, HCC, or a positive ratio for each stratified group is expressed as a percentage of the total patient number. Statistical comparisons were made using Pearson's chi-square test to compare the effects of gender and positive ratio of each stratified group. Independent T test was used to analyse age, ALT and HCV viral load. A p-value below 0.05 was considered statistically significant.

Results

Amongst all 81 subjects, there were 60 (74.1%) and 21 (25.9%) chronic HCV genotype 1b-infectied cases belonging to the Pro-D group and the DCV/ASV group. The general data is shown in Table 1. The age and gender were similar between these two groups. On the contrary, a significantly higher rate in the individuals with Pro-D had prior treatment experience to IFN (75%) comparing with those with DCV/ASV (75% *vs.* 52.4%, p=0.009). A mildly higher portion of cases in the DCV/ASV group had an appearance of both cirrhosis (52.4%) and HCC (38.1%).

	Pro-D (N=60)					**DCV/ASV (N=21)**					**P-value**
	M	±	SD	N	%	M	±	SD	N	%	
Age (years)	66.5	±	10.08			64.14	±	10.79			0.862 b
Gender											0.333 a
Male				28	-46.70%				9	-42.90%	
Female				32	-53.30%				12	-57.10%	
Treatment experience#				45	-75.00%				11	-52.40%	0.009 a
Cirrhosis				20	-33.30%				11	-52.40%	0.155 a
HCC				17	-28.30%				8	-38.10%	0.545 a
a=Pearson's Chi-square test, b=independent T test.											
Abbreviations: ASV: Asunaprevir; DCV: Daclatasvir; HCC: Hepatocellular Carcinoma; M: Mean; N: Number of patients; Pro-D: Paritaprevir/ritonavir/ombitasvir +dasabuvir; SD: Standard Deviation.											
# to IFN											

Table 1: The general data of the patients according to age and gender of the patients.

	Pro-D (N=60)			DCV/ASV (N=21)			P-value
	M	N	%	M	N	%	
Pre-treatment ALT (U/L)	113.2			116.9			0.564 b
Pre-treatment HCV RNA (x106 IU/ml)	2.94			1.39			0.148 b
DAAs efficacy							
VR4		57	-95.00 %		19	-90.50 %	0.695 a
EOTVR		59	-98.30 %		19	-90.50 %	0.183 a
SVR12		59	-98.30 %		19	-90.50 %	0.183 a
a=Pearson's Chi-square test, b=independent T test. Abbreviations: ALT: Alanine Aminotransferase; ASV: Asunaprevir; DAAs: Direct Acting Antivirals; DCV: Daclatasvir; EOTVR: End-of-Treatment Virologic Response; M: Mean; N: Number of Patients; Pro-D: Paritaprevir/ritonavir/ombitasvir+dasabuvir; SD: Standard Deviation; SVR: Sustained Virologic Response; VR: Virologic Response.							

Table 2: The status of HCV and DAAs therapeutic effectiveness of patients.

The HCV status and DAAs therapeutic effectiveness is displayed in Table 2. A high HCV viral load with an elevated serum ALT was found before DAAs started (mean HCV RNA 1.39 -2.94 × 10^6 IU/ml, mean ALT 113.2-116.9 U/L). There were 1 and 2 cases with Pro-D and DCV/ASV respectively, failing to achieve EOTVR and SVR12. The rate of EOTVR and SVR12 of the Pro-D group and the DCV/ASV group were 98.3% and 90.5%, respectively. These differences were not significant (p=0.183).

The detailed data about the cases where DAAs treatment failed are listed in Table 3. The first one is a 46-year-old, treatment-naïve, cirrhotic man, scheduled for 3-month therapy with Pro-D. The patient failed in achievement of EOTVR and SVR12 due to persistent HCV viremia (HCV RNA 50,000 and 30,000 IU/ml at the end and after 3 months of Pro-D treatment, respectively). The second one was a 42-year-old, treatment-naïve, cirrhotic woman, where a 6-month therapy schedule with DCV/ASV was planned. The treatment was terminated early due to persistent HCV viremia during the first 2 months after DCV/ASV had begun (HCV RNA 54,400 IU/ml after 2 months of

DCV+ASV treatment). The final one was a 46-year-old, treatment-naïve, non-cirrhotic man, where 6-month therapy with DCV/ASV was scheduled. The treatment failed due to the reappearance of HCV RNA after 5 months of DCV/ASV treatment (HCV RNA 30,200 IU/ml), and the rechecking of the HCV genotype reported a mixed Ia and Ib infection [5].

	Case 1	Case 2	Case 3
Age (years)	46	42	46
Gender	male	female	male
Treatment experience#	no	no	no
Cirrhosis	yes	yes	no
HCV genotype	1b	1b	1b
NS5A RAS*	no	no	no
Pre-treatment HCV RNA (x106 IU/ml)	2.37	1.04	3.07
Scheduled DAAs regimen	Pro-D, 12 weeks	DCV/ASV, 24 weeks	DCV/ASV, 24 weeks
VR4	no	no	yes
EOTVR	no	no	no
SVR12	no	no	no
Courses of treatment failure	Persistent HCV viremia during and after DAAs treatment	Persistent HCV viremia at the 2 month after DAAs start.	Reappearance of HCV viremia at the 5 months after DAAs start.

Abbreviations: ALT: Alanine Aminotransferase; ASV: Asunaprevir; DAAs: Direct Acting Antivirals; DCV: Daclatasvir; EOTVR: End-of-Treatment Virologic Response; M: Mean; N: Number of patients; Pro-D: paritaprevir/ritonavir/ombitasvir+dasabuvir; NS5A: Nonstructural Protein 5A; RAS: Resistance-Associated Substitutions; SD: Standard Deviation; SVR: Sustained Virologic Response; VR: Virologic Response.# to IFN; * positions L31 and Y93

Table 3: The detailed data about the cases where DAAs treatment failed.

The changes of serum ALT and bilirubin in the Pro-D group and the DCV/ASV group are shown in Figures 1 and 2, respectively. For the cases which underwent Pro-D treatment, the ALT level of each individual remained normal after treatment start, however the mean serum bilirubin increased, with a peak happening at 2 weeks of Pro-D treatment. For the subjects with DCV/ASV, an elevation of ALT was noted at 3 months of treatment; while no accompanying changes in the bilirubin level was found.

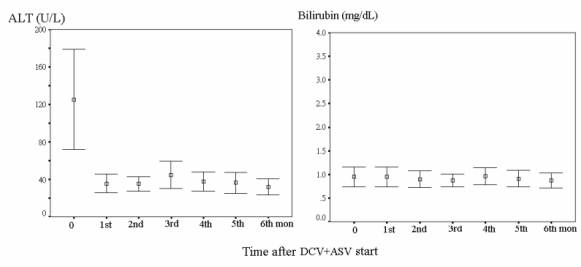

Figure 1: The change in liver function during the therapy with Daclatasvir (DCV)/ Asunaprevir (ASV)

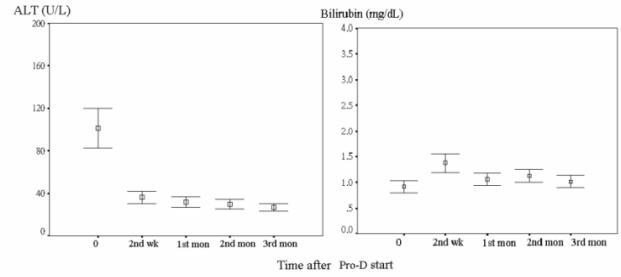

Figure 2: The change in liver function during the therapy with Paritaprevir/ritonavir/ombitasvir+Dasabuvir (Pro-D)

The levels of bilirubin in the cases which had undergone Pro-D treatment with or without cirrhosis are displayed in Figure 3. Whether having cirrhosis or not, the peak elevation of bilirubin both occurred at 2 weeks of Pro-D treatment. There were no differences among these two subgroups. For all the cases in our study, the grades of adverse effects associated with DAAs were generally mild, and no patients required drug dosage adjustment.

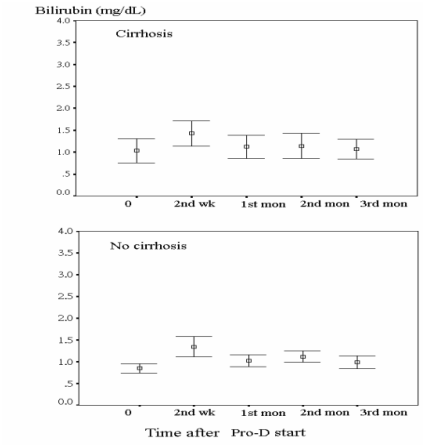

Figure 3: The change in bilirubin during the therapy amongst cirrhotic and non-cirrhotic subjects with Paritaprevir/ritonavir/ombitasvir+Dasabuvir (Pro-D).

Discussion

Chronic HCV infection is affecting approximately 130 to 150 million individuals worldwide. In the past, the combination of IFN and RBV was the only approved treatment for chronic HCV; however this treatments limitation included low efficacy and treatment-associated adverse events. Recently, therapeutic regimens for patients with chronic HCV infection have been altered through the use of oral DAAs [1].

In Taiwan and other East Asian countries, HCV subtype 1b is most predominant [2]. The ratio of HCV-1b in Taiwan is 45.5%~71.4% among all cases with HCV infection [6,7]. DAAs regimens, including elbasvir/grazoprevir, sofosbuvir/ledipasvir, DCV/ASV and Pro-D have been approved for the treatment of patients with HCV-Ib infection in Taiwan. The rates of SVR12 for Pro-D over a 12-week period are 96.7%-100% and 98.5%-100%, in non-cirrhotic and cirrhotic HCV-1b patients respectively [8,9]. The response rate (SVR12 or 24) for DCV/ASV is 90% of the treatment-naive cohort, and 82%-87.4% in the treatment-experience cohort [10].

However, due to the highly selective patient populations included in the clinical trials, the applicability of these results to routine clinical practice may have limitations. Thus, real-world data is needed to both confirm clinical trial findings and guide treatment decisions.

One large Spanish cohort involving 1,567 patients, most (83.7%) who belonged to the HCV genotype 1b-infection group; reported a SVR12 rate of 96.8% with Pro-D, and 95.8% with sofosbuvir/ledipasvir. Among all the 13 subjects with virologic failure, 3 (72.3%) cases relapsed after end-of-treatment, while 5 (27.7%) experienced on-treatment virologic breakthrough [11]. Another US cohort which enrolled 297 cases with Pro-D, the SVR rate was 98% for the subjects undergoing Pro-D treatment. High values of fibrosis-4 (FIB-4) index and body mass index (BMI) were negative predictors for the SVR rate [12].

A review article involving nine trials (n=1,690), found SVR12 of DCV/ASV was achieved by 89.9% of treatment-naive patients, 84.7% of interferon-intolerant patients, and 81.9% of nonresponsive patients. Baseline characteristics, including gender, race, advanced age, non-CC IL28B genotype, and cirrhosis, did not appear to impact SVR rates. Among patients with NS5A resistance-associated substitutions (RAS) at baseline, only 51.2% (86/168) and 41.9 (26/62) of the patients were able to achieve SVR12 and SVR24, respectively. Therefore, pre-existing NS5A RAS was associated with virological failure during DCV/ASV therapy [4].

In our study, the subjects receiving Pro-D and DCV/ASV numbered 60 and 21 cases, respectively. The difference in case numbers may be due to the therapeutic time duration (Pro-D of 12 weeks and DCV/ASV of 24 weeks). The rate of SVR12 for the subjects undergoing treatment with Pro-D and DCV/ASV were 98.3% and 90.5%, respectively. These rates are similar with previous results of clinical trials and real-world studies. Among the 3 cases with virologic failure, two had persistent viremia and one experienced a reappearance of viremia. Neither baseline nor within-therapeutic NS5A RAS was absent. All cases achieving EOTVR could remain positive with SVR12. Due to our limited cases involving virologic failure, there were no identified predictors for DAAs treatment failure, and further investigation is still required.

In a phase-3 trial in Japan, of the 222 subjects enrolled who underwent DCV/ASV treatment, 35 of the 222 cases (15.8%) had an increased ALT observed during their therapeutic period, with 10 cases discontinuing treatment [13]. Our data showed an elevated ALT whose peak occurred at the third month of DCV/ASV treatment, where no one needed to discontinue treatment.

Due to probable inhibition in bilirubin transporters OATP1B1 and OATP1B3 by paritaprevir, hyperbilirubinemia happening during Pro-D treatment was well-known. Pro-D associated liver failure has been previously reported [14]. A recent study has indicated that a major predictive factor of incident decompensation is a previous history of decompensated cirrhosis [15]. The cohort in Taiwan found 23.3% of patients having an elevation of bilirubin during Pro-D treatment, where only one case had to cease Pro-D due to appearing signs of liver failure. The absolute bilirubin level was higher in cirrhotic subjects than non-cirrhotic ones [16].

Our cases found that the peak serum bilirubin level occurred at the second week of Pro-D treatment, with no one developing liver failure, implying that Pro-D need not be discontinued. Additionally, the highest values of bilirubin were similar between the cirrhotic and non-cirrhotic cases.

There were several limits in our study. First, this study was a retrospective and presented to at a single tertiary care centre. Selection bias may have existed and thus could not reflect the all population. Second, the small number within our study may offer unreliable estimations of the results. Third, liver function parameters were monitored every two weeks in our study, and more frequent examinations may be required for some at risk patients, such as those with a previous history of decompensated cirrhosis. Finally, the retreating regimens for cases with DAA virologic failure were not determined. Further research and analysis, with the use of more variables is needed.

Conclusion

In conclusion, our study found SVR12 after treatment with Pro-D and DCV/ASV were 98.3% and 90.5%, respectively. Elevated levels of

ALT and bilirubin occurred at the third month of DCV/ASU treatment and the secondary weeks of Pro-D treatment, respectively.

References

1. Ghany MG, Strader DB, Thomas DL, Seeff LB (2009) Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 49: 1335-1374.
2. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H (2014) Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 61: S45-S57.
3. AASLD/IDSA HCV Guidance Panel (2015) Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 62: 932-954.
4. Nam HC, Lee HL, Yang H, Song MJ (2016) Efficacy and safety of daclatasvir and asunaprevir for hepatitis C virus genotype 1b infection. Clin Mol Hepatol 22: 259-266.
5. Lee SW, Yang SS, Lee TY, Yeh HZ, Lu IT, et al. (2017) Oral direct acting antivirals treatment failed to cure a patient with chronic hepatitis C due to shifts of viral genotype. J Gastrointestin Liver Dis 26: 205-206.
6. Kao JH, Chen PJ, Lai MY, Yang PM, Sheu JC, et al. (1995) Genotypes of hepatitis C virus in Taiwan and the progression of liver disease. J Clin Gastroenterol 21: 233-237.
7. Lee CM, Lu SN, Hung CH, Tung WC, Wang JH, et al. (2006) Hepatitis C virus genotypes in southern Taiwan: prevalence and clinical implications. Trans R Soc Trop Med Hyg. 100: 767-774.
8. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, et al. (2014) ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 370: 1973-1982.
9. Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, et al. (2014) ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 147: 359-365.
10. Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, et al. (2014) All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet 384:1597-1605.
11. Calleja JL, Crespo J, Rincón D, Ruiz-Antorán B, Fernandez I, Perelló C, et al. (2017) Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: Results from a Spanish real-world cohort. J Hepatol 66: 1138-1148.
12. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA (2016) Comparative effectiveness of ledipasvir/sofosbuvir ± ribavirin vs. ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin in 6961 genotype 1 patients treated in routine medical practice. Aliment Pharmacol Ther 44: 400-410.
13. Kumada H, Suzuki Y, Ikeda K, Toyota J, Karino Y, Chayama K, et al. (2014) Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. Hepatology 59: 2083-2091.
14. Masetti M, Magalotti D, Martino E, Andreone P, Scuteri A, et al. (2016) A case of acute liver failure during ritonavir-boosted paritaprevir, ombitasvir and dasabuvir therapy in a patient with HCV genotype 1b cirrhosis. J Gastrointestin Liver Dis 25: 559-561.
15. Flisiak R, Janczewska E, Wawrzynowicz-Syczewska M, Jaroszewicz J, Zarezbska-Michaluk D, et al. (2016) Real-world effectiveness and safety of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in hepatitis C: AMBER Study. Aliment Pharmacol Ther 44: 946-956.
16. Liu CH, Liu CJ, Su TH, Yang HC, Hong CM, et al. (2018) Real-world effectiveness and safety of paritaprevir/ritonavir, ombitasvir, and dasabuvir with or without ribavirin for patients with chronic hepatitis C virus genotype 1b infection in Taiwan. J Gastroenterol Hepatol 33: 710-717.