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Efficacy of Fixed-dose Combination of Sofosbuvir and Ledipasvir (SOF/LDV) ± Ribavirin (RBV) in Patients (n=130) Infected with HCV Genotype 6 (Real World Myanmar Experience)

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Abstract:

Background: The prevalence rate of HCV Genotype 6 is estimated to account for 36% of all HCV infections in Myanmar.

Objective: This study is aimed to assess the efficacy of SOF/LDV ± RBV in patients infected with HCV genotype 6.

Methods: We performed the prospective and observational study of 130 patients infected with chronic HCV genotype 6 (both treatment-naïve and treatment-experienced) was performed. The patients were treated with SOF/LDV ± RBV for 12 or 24 weeks.

Results: Overall SVR (sustained virologic response) rate was 77% of patients. Higher SVR rate was noted among the cirrhotic patients (p-value = 0.003) and treatment-experienced patients (p-value = 0.008). Co-infection with HBV was seen in 7 patients and all these patients achieved SVR12. In the study cohort, 104 patients were treatment-naïve and 26 patients were treatment-experienced. SVR rates of treatment-naïve patients with or without cirrhosis treated with SOF/LDV regimen for 12 weeks was 65% (n=47), SOF/LDV/RBV for 12 weeks was 82% (n=9) and SOF/LDV for 24 weeks was 91% (n=19). Twenty-six treatment-experienced patients were treated with SOF/LDV/RBV for 24 weeks and achieved 96% SVR rate.

Conclusion: SOF/LDV ± RBV therapy achieved SVR12 in 77% of all categories of genotype 6 patients demonstrating the unsatisfactory response and efficacy in the era of SVR rates approaching 100% in other genotypes. Therefore, our real-life experience showed genotype 6 as the most difficult to treat genotype. However, it was noted that the addition of RBV or extension of treatment duration can increase the SVR rates significantly.

Keywords: Hepatitis C virus, genotype 6, sofosbuvir, ledipasvir, ribavirin

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Introduction

Globally, an estimated 71 million people have chronic hepatitis C infection. A significant number of those who are chronically infected will develop cirrhosis or liver cancer. Approximately 399,000 people die each year from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma[1]. HCV Genotypes 1, 2 and 3 are widely distributed globally and Genotypes 4 and 5 are found mainly in Africa and Middle East. Genotype 6 is major genotype distribution in Southeast Asia especially in Thailand, Vietnam and Myanmar, detected in 10-60% of all HCV patients[2]. In Myanmar, HCV genotype 6 is the one of the most prevalent accounting 49% of all HCV patients. Regarding genotype distribution in Myanmar, HCV genotype 6 was the most prevalent genotype (49%), followed by HCV genotypes 3 (39%), 1 (11%), and 2 (0.7%)[3]. In Myanmar, HCV genotype 6 was most often found in patients in the northern cities and HCV genotype 3 in the southern and western cities, suggesting that there are regional differences in HCV genotype distribution[3].

In recent years, the development of drugs that directly interfere with HCV replication has changed the landscape of HCV treatment and there are now effective combinations of direct-acting antiviral agents for most patients. Ledipasvir (Gilead Sciences) is a new HCV NS5A inhibitor and Sofosbuvir is a nucleotide analogue inhibitor of the HCV NS5B polymerase approved for the treatment of HCV in combination with NS5A inhibitor such as ledipasvir, and ribavirin.

For the treatment-naïve HCV genotype 6 patients, APASL (Asian Pacific Association for the Study of the Liver) recommend SOF/LDV without ribavirin for 12 weeks in patients with no cirrhosis (evidence level – B1) and SOF/LDV with ribavirin for 12 weeks for those with compensated cirrhosis (evidence level – B1)[4].

According to EASL (The European Association for the Study of the Liver) HCV Guidelines 2016, treatment-naïve patients infected with genotype 6 with or without compensated cirrhosis can be treated with SOF/LDV without ribavirin for 12 weeks (evidence level – B1). And treatment-experienced patients with or without compensated cirrhosis should be treated with SOF/LDV with ribavirin for 12 weeks (evidence level – B1)[5].

AASLD (American Association for the Study of the Liver Diseases) 2016 Guidelines recommend that treatment-naïve patients with or without cirrhosis should be treated with SOF/LDV for 12 weeks (Rating – Class IIA, Level B). For Peg-IFN/SOF-experienced patients with or without cirrhosis should be treated with SOF/LDV 12 weeks (Rating – Class IIA, Level B)[6].

Although HCV Genotype 6 is encountered predominately in Southeast Asia, data on optimal treatment strategy is limited. Fixed-dose combination of sofosbuvir and ledipasvir (SOF/LDV) is the first all-oral DAA (direct acting antiviral) approved for HCV Genotype 6. For the optimal treatment regimen for the patients with genotype 6, the international treatment guidelines such as APASL, AASLD, and EASL guidelines are followed and at the time of this study, SOF/LDV with or without ribavirin is the regimen of choice for the HCV genotype 6. But the evidence grading of these guidelines are not strong enough to adopt the most effective guidelines for the resource-limited country like Myanmar. Therefore, this study is aimed to assess the efficacy of available generic version of fixed-dose combination of Sofosbuvir

(400 mg) and Ledipasvir (90 mg) (SOF/LDV) with or without ribavirin in Myanmar patients infected with HCV genotype 6.

Methods

This is the open-label, real-world prospective non-randomized observational study conducted at a single centre, Yangon GI and Liver Centre, in Yangon, Myanmar from January 2016 to September 2017 as an investigator-initiated study. In this single-centre study, all the patients received a fixed-dose combination tablet containing 400 mg of sofosbuvir and 90 mg of ledipasvir, administered orally once daily. Ribavirin was administered orally twice daily, with the dose determined according to body weight (1000 mg daily in patients with a body weight <75 kg, and 1200 mg daily in patients with a body weight ≥75 kg).

In Myanmar, the available generic versions of SOF/LDV (400mg/90mg) are Ledifos® manufactured by Hetero, LediHep® by Zydus and MyHep LVIR® by Mylan. The monthly cost of generic SOF/LDV/RBV combination therapy varies between 250-300 USD with different manufacturers from India, Pakistan, and Bangladesh. As Myanmar does not have the National Health System nor the medical insurance system, the medications and investigations were paid for by the patients themselves and informed consents were taken from all patients.

SOF/LDV without ribavirin for 12 weeks was given in treatment-naïve patients without cirrhosis. Treatment-naïve patients with compensated cirrhosis were given SOF/LDV with ribavirin for 12 weeks or 24 weeks without ribavirin if ribavirin was ineligible or if patients were intolerant to ribavirin. PEG-IFN/RBV-experienced patients with or without compensated cirrhosis were treated with SOF/LDV with ribavirin for 24 weeks.

Patients

Total 130 patients infected with chronic HCV genotype 6 (both treatment-naïve and treatment-experienced) were enrolled. Eligible patients were men and women who were older than 12 years old, who had serum HCV RNA level > 25 IU/mL with HCV genotype 6, patients with or without compensated cirrhosis, treatment-naïve patients and those who relapsed after PEG-IFN/RBV-containing regimen. Patients with hepatitis B virus (HBV) co-infection and/or human immunodeficiency virus (HIV) co-infection were included in the study. Patients were excluded if they were pregnant, willing to conceive in the near feature, or lactating and if they had chronic kidney disease with creatinine clearance < 30 mL/min as estimated by the Cockcroft-Gault method. Patients with significant medical co-morbidities such as ischemic heart diseases, chronic pulmonary diseases, psychiatric disorders and hepatocellular carcinoma (HCC) were also excluded from the study.

HCV Genotype were analyzed by the use of the Roche® cobas® 4800 system. The presence of cirrhosis or advanced fibrosis (F3/F4) was assessed using Fibroscan® (Echosense, France), abdominal ultrasonography, aspartate aminotransferase: platelet ratio index (APRI), and clinical evaluation. The presence of cirrhosis was defined as a FibroScan score of more than 12.5 kPa (on a scale of 1.5 to 75.0 kPa, with higher scores indicating a greater degree of fibrosis) and/or an APRI of more than 2 (with higher scores indicating a greater likelihood of extensive fibrosis).

Assessments

HCV viral loads were analyzed by Roche® COBAS® HCV quantitative nucleic acid test 4800 system, COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Assay. The lower limits of detection and quantification were 15 IU per milliliter and 25 IU per milliliter, respectively. Serum HCV RNA levels were measured at baseline, week 4, 12, 24 (if applicable) and 12 weeks after the end of treatment.

Patients were evaluated clinically along with laboratory testing, at entry and every 4 weeks during treatment and 12 weeks after the end of treatment to assess safety of treatment. Assessments during treatment included standard laboratory testing, serum HCV RNA, vital signs, electrocardiography, and symptom-directed physical examinations. All adverse events were recorded and graded according to a standardized scale. Anemia was defined as mild (hemoglobin (Hb) values between 10-12 g/dL), moderate (Hb values between 8.5-10 g/dL), or severe (Hb values less than or equal to 8.5 g/dL). Occurrence of anemia during treatment was managed by 200 mg RBV dose reduction, use of erythropoietin, and/or blood transfusions.

Outcomes and endpoints

The primary efficacy end point was the rate of sustained virologic response (SVR), defined as the absence of quantifiable HCV RNA in serum (<25 IU per milliliter), at 12 weeks after the end of therapy (SVR12) among all patients. Virologic relapse was defined as a confirmed HCV RNA level of 25 IU per milliliter or more 12 weeks after receipt of the last dose of drug among patients who completed treatment.

Statistical analyses

Data analysis was done by SPSS software (v.16). The data were described using counts and proportions for categorial data and mean ± standard deviation if the data showed a non-parametric distribution. Categorical data were calculated by Chi-square and Fisher's Exact Test. Continuous data was calculated by ANOVA (Analysis of Variance). The level of statistical significance was set at a two-tailed p-value of < 0.05.

Study oversight

This study received approval from the Institutional Review Board or independent ethics committee to review the data for publication purposes and was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines and local regulatory requirements. The investigators agreed to maintain confidentiality of the data and all the authors had access to the data and assume responsibility for the integrity and completeness of the reported data.

Results

Demographics and baseline characteristics

Total of 145 patients were screened for this study and received the fixed-dose combination of sofosbuvir and ledipasvir (SOF/LDV) with or without ribavirin for 12 or 24 weeks according to the cirrhosis status and the treatment history, at Yangon GI and Liver Centre, between January 2016 and September 2017. Among them, 15 patients were excluded because of the

Table 1 Baseline demographic and laboratory characteristics

Characteristics	12-week regimen		24-week regimen		p-value
	SOF/LDV x 12 weeks (n = 72)	SOF/LDV/ RBV x 12 weeks (n = 11)	SOF/LDV x 24 weeks (n = 21)	SOF/LDV/RBV x 24 weeks (n = 26)	
Age – years					
Mean	50.9 (±12.1)	55.8 (±13.2)	54.5 (±11.1)	57.1 (±8.8)	0.88
Range	15 – 76	27 – 72	26 – 69	37 – 79	
Body Mass Index – kg/m²					
Mean	22.6 (±2.9)	21.5 (±2.0)	22.3 (±3.0)	24.6 (±3.0)	**0.007**
Range	18 – 31	19 – 26	19 – 28	20 – 32	
Sex – n (%)					
Male	37 (51)	3 (27)	8 (38)	5 (19)	0.174
Female	35 (49)	8 (83)	13 (62)	21 (81)	
Subtype of Genotype 6 – n (%)					
Subtype 6 n	4 (6)	1 (9)	1 (5)	6 (23)	
Subtype 6 m	8 (11)	2 (18)	-	-	**0.017**
Subtype 6 cL	47 (65)	8 (73)	19 (90)	14 (54)	
Unspecified	13 (18)	-	1 (5)	6 (23)	
HCV RNA (Quantitative Viral Load)					
≥ 800,000 IU/mL	53	9	14	15	0.367
< 800,000 IU/mL	19	2	7	11	
Cirrhosis status – n (%)					**< 0.0001**
No cirrhosis	72 (100)	-	-	5 (20)	
With compensated cirrhosis	-	11 (100)	21 (100)	21 (80)	
HCV/HBV Co-infection	4	1	-	2	0.622
ALT – IU/mL, mean (±SD)	53.8 (±35.1)	59.0 (±35.0)	74.7 (±55.3)	66.3 (±37.0)	0.149
Total Bilirubin – mg/dL, mean (±SD)	0.85 (±0.48)	1.62 (±3.0)	1.07 (±0.64)	1.16 (±1.08)	0.138
Albumin – g/dL, mean (±SD)	5.5 (±0.9)	3.4 (±0.4)	3.5 (±0.4)	3.4 (±0.5)	0.606
Hemoglobin – g/dL, mean (±SD)	13.1 (±1.8)	12.4 (±0.9)	12.6 (±1.3)	12.4 (±2.2)	0.233
Platelets count – 10^9/L, mean (±SD)	226.8 (±72.1)	173.4 (±56.4)	146.4 (±50.6)	187.0 (±126.0)	**0.001**
AFP – IU/mL, mean (±SD)	6.2 (±7.8)	4.6 (±2.3)	6.8 (±4.8)	8.0 (±5.4)	0.499
Creatinine* – mg/dL, mean (±SD)	0.97 (±0.30)	1.00 (±0.71)	0.90 (±0.30)	0.98 (±0.28)	0.961

Data expressed as mean ± SD or number (%)
SOF = Sofosbuvir, LDV = Ledipasvir, RBV = Ribavirin, ALT = Alanine aminotransferase, AFP = Alpha-fetoprotein
*Estimated by the Cockcroft-Gault method

insufficient follow-up and incomplete treatment. Table 1 shows the baseline demographic and laboratory characteristics of the remaining 130 patients classified by the different treatment regimens.

The mean age at the time of treatment initiation was 53.2 years (SD = 11.6) and 43% of patients were male (n=56) and 57% were female (n=74). The majority of patients were treatment-naïve (80%, n=104) and 26 patients (20%) had a history of previous PEG-IFN/RBV therapy. About 40% (n=53) of patients had cirrhosis at the time of treatment initiation. The median BMI (Body Mass Index) of the entire group was 22.9 kg/m^2 (SD = 3.0). The mean baseline viral load prior to start of treatment was 3.3 million IU/mL (range 11,000 to 22,322,717) with 61 patients (48%) who had HCV RNA ≥ 800,000 IU/mL.

Regarding the pre-treatment liver functions assessment, the pretreatment mean albumin level was 4.0 g/dL (SD = 0.4), the mean total bilirubin was 1.0 mg/dL (SD = 1.1), and the mean platelet count was 201 x 10^9/L (SD = 86.9). The mean serum creatinine level was 0.97 mg/dL (SD = 0.3), and the mean AFP (Alpha-Feto Protein) level was 6.5 IU/mL (SD = 6.6).

Among all the patients, 7 patients were co-infected with chronic hepatitis B infection. of these HCV/HBV co-infected patients, 5 were treatment-naïve and 2 had the history of previous PEG-IFN/RBV therapy. All 7 patients co-infected with HCV/HBV achieved SVR12.

Efficacy

Overall SVR rates of entire group was 77% (n = 100). Among the patients who reached SVR 12, males were 43% (n = 43/100) and females were 57% (n = 57/100). The higher SVR rate (90%) was noted among the cirrhotic patients (n = 48/53) than cirrhotic patients (68%, n = 52/77). Among the treatment-naïve patients (n = 104), 75 patients (72%) achieved SVR whereas 25 out of 26 treatment-experienced patients (96%) achieved SVR 12. The patients with baseline HCV RNA viral load < 800,000 IU/mL achieved SVR rate of 59% (n = 59/100) whereas among those with viral load ≥ 800,000 IU/mL, there were 41% of patients (n = 41/100) who achieved SVR 12. Table 2 shows the overall treatment outcomes of patients infected with HCV genotype 6.

Moreover, SVR rates were analyzed according to the treatment regimens. Of the entire group, 72 treatment-naïve patients without cirrhosis received SOF/LDV for 12 weeks, resulting in 65% SVR rate (n = 47). Remaining 32 treatment-naïve patients with compensated cirrhosis received SOF/LDV for 24 weeks (n = 21) (if they are ribavirin-ineligible or ribavirin-intolerant) and SOF/LDV with ribavirin for 12 weeks (n = 11). 91% of patients (n = 19) achieved SVR 12 among those who received SOF/LDV without ribavirin for 24 weeks and 82% (n = 9) achieved SVR 12 in patients who received SOF/LDV with ribavirin for 12 weeks. For the participants who had a treatment history with PEG-IFN/RBV, SOF/LDV with ribavirin for 24 weeks was adopted. Among these 26 treatment-experienced patients, 25 patients (96%) achieved SVR 12 and only one patient relapsed. Table 3 and Figure 1 show the SVR rates according to the different treatment regimens.

Safety

The patients were well-tolerated to drugs and no one discontinued the treatment through the study. There were no incidents of serious adverse events and no discontinuation of treatment due to adverse events during the course of this study. The most frequently reported side effects were fatigue (20%) and anemia (17%). Majority of these side effects were reported by patients who received the treatment regimen containing ribavirin. Among the entire group, the dose of ribavirin had to be reduced in 16 patients (12%) and only 6 patients needed the erythropoietin-stimulating agents for the correction of anemia but no blood transfusions were necessary.

Discussion

This study of efficacy of generic version of SOF/LDV with or without ribavirin in the treatment of patients with chronic HCV genotype 6 is one of the largest real-world studies. Higher SVR rates of have been reported with the all oral combination of SOF/LED for 12 weeks in a clinical trial and real-world Vietnamese study[7,8]. However, in our study, treatment with the once-daily, interferon-free, single-tablet regimen of SOF/LDV ± RBV resulted in a sustained virologic response in 77% of patients with HCV genotype 6. Therefore, the SVR rates in our study were somewhat lower than those reported.

Table 2 Overall outcomes of HCV genotype 6 patients

		SVR 12 Achieved		SVR 12 Not achieved		p-value
		Number	%	Number	%	
Overall		**100**	**77**	**30**	**23**	
Sex	Male	57	57	13	43	1.000
	Female	43	43	17	57	
Cirrhosis status	Cirrhosis	48	48	5	17	**0.003**
	No cirrhosis	52	52	25	83	
Treatment History	Treatment-naïve	75	75	29	97	0.008
	Treatment-experienced	25	25	1	3	
0.831BMI	BMI < 25	74	74	24	80	0.684
	BMI ≥ 25	26	26	6	20	
Subtype of HCV genotype 6	Subtype 6 n	8	8	4	13	0.831
	Subtype 6 m	8	8	2	7	
	Subtype 6 cL	68	68	20	67	
	Unspecified	16	16	4	13	
HCV RNA	< 800,000 IU/mL	59	59	2	7	**0.000**
	≥ 800,000 IU/mL	41	41	28	93	

Data expressed as n and %
SVR12 = sustained virologic response at 12 weeks after the end of therapy

Throughout the development of HCV therapy, cirrhosis remains to indicate low rates of response in regimens that include SOF, LDV or DCV[9]. But, one of the important findings of our study was that cirrhotic patients achieved about 90% SVR with SOF/LDV/RBV for 12 weeks or SOF/LDV for 24 weeks regimens. Prior studies revealed that treatment-experienced patients reached lower SVR rates[10]. However, in our study, patients who had the previous treatment history had greater SVR rates (96%, n=26/25) compared to treatment-naïve patients (72%, n=75/104). These study results could be justified by the addition of ribavirin and the extension of treatment duration up to 24 weeks in treatment-experienced patients.

There were a significant association between SVR and each treatment regimen (p =0.004). But no conclusion regarding the superiority of the treatment regimen containing ribavirin over the regimen without ribavirin could be made due to the observational nature of our study. Our study results suggested that the addition of ribavirin improved the efficacy of SOF/LDV in the treatment of HCV genotype 6 patients. Also, treatment-experienced patients with or without compensated cirrhosis received SOF/LDV/RBV for 24 weeks, so groups that received 12 or 24 weeks of SOF/LDV/RBV were not comparable. Therefore, assessment between treatment duration could not be done. However, according to our real world Myanmar experiences, the addition of ribavirin to regimen of SOF/LDV and/or

Table 3 SVR rates by treatment regimens of patients with HCV genotype 6

	Regimens								p-value
	SOF/LDV x 12 weeks		SOF/LDV/RBV x 12 weeks		SOF/LDV x 24 weeks		SOF/LDV/RBV x 24 weeks		
	No.	%	No.	%	No.	%	No.	%	
SVR Achieved	47	65	9	82	19	91	25	96	**0.004**
Virologic Failure	25	35	2	18	2	9	1	4	

Data expressed as n and %

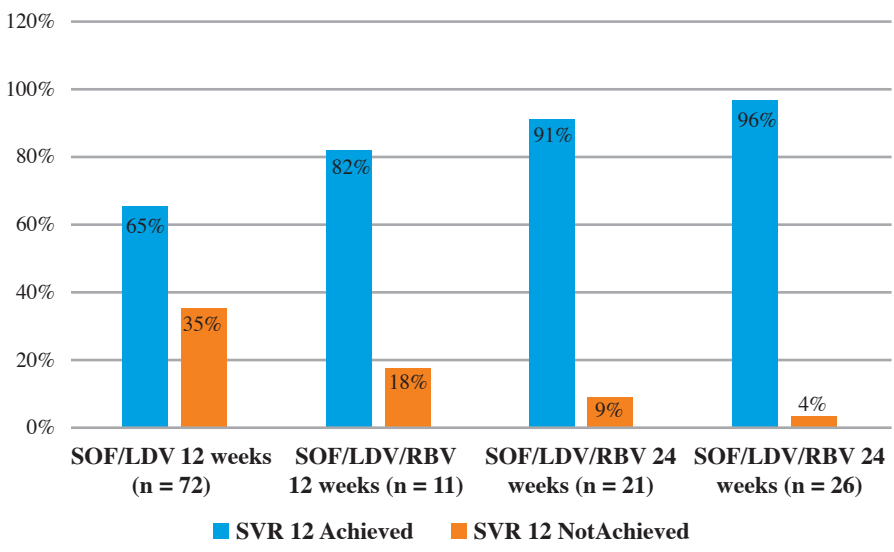

Figure 1 SVR rates by treatment regimens of patients with HCV genotype 6

extension of treatment duration may increase the SVR rates and this should be applied for the guidance of management of HCV genotype 6 patients.

When the data were analyzed by the subtypes of HCV genotype 6, there were 67% (n=20/30) of subtype 6-cL patients who had virologic failures. Thus, another finding of our study is that subtype 6-cL is the most common and difficult to treat subtype in Myanmar although this is not statistically significant.

The most common adverse effects in our study were fatigue, insomnia, and headache. While 17% of patients experienced adverse effects that led to modification and/or interruption of ribavirin, no one discontinued treatment suggesting that ribavirin was tolerable in most patients. Therefore, SOF/LDV ± RBV was safe and well-tolerated with the safety profile consistent with the known effects of ribavirin.

This study has the limitations related to its open-label, non-randomized and observational nature and real-world design including potential physician prescribing bias, local practice discrepancies, and data entry errors. Another limitation of our study is that we do not have analysis of virologic failures but we expected that treatment failures would be predominantly associated with resistance-associated variants.

Conclusion

Among a large cohort study of chronic HCV genotype 6, treatment with all-oral SOF/LDV achieved SVR 12 in 77% of patients, demonstrating the unsatisfactory response and efficacy of this treatment regimen in Myanmar. Therefore, it can be concluded that according to Myanmar experience of 130 patients, genotype 6 was found to be most difficult

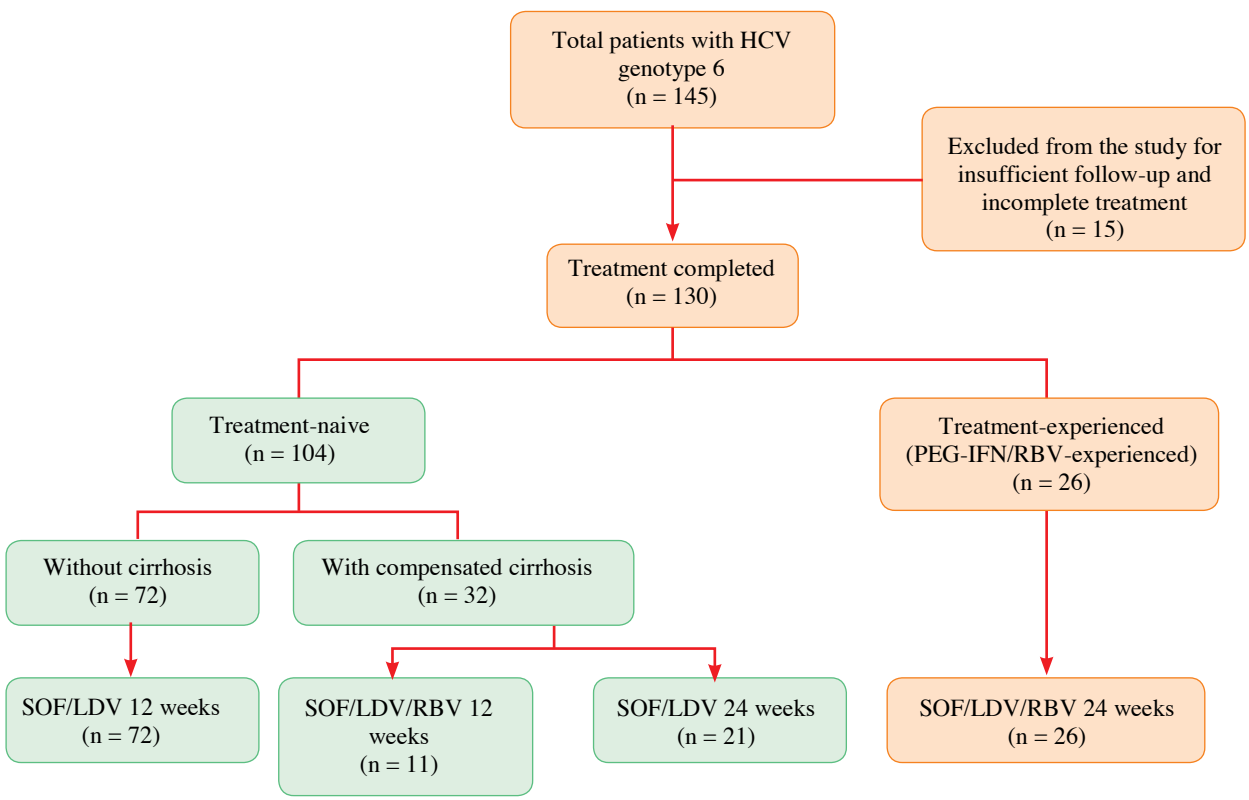

Figure 2 Flow Chart – Outline of the study treatment scheme for patients

to treat genotype. The increased efficacy will be achieved with addition of RBV to SOF/LDV and/or extension of treatment duration or more effective and pan-genotypic regimen such as sofosbuvir and velpatasvir.

Conflict of interest

All authors do not have any conflict of interest.

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