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Efficacy of *Velpatasvir Sofosbovir* alone Versus in Combination with Ribavarin in Cirrhotic Patients with Hepatitis C

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ABSTRACT

Background: Chronic Hepatitis C (HCV) infection is a major cause of liver cirrhosis and its complications. Direct-acting antivirals (DAAs) such as sofosbuvir and velpatasvir have shown high efficacy in treating HCV, but the additional role of ribavirin in combination therapy remains uncertain, particularly in cirrhotic patients. **Objective:** This study compares the efficacy and safety of sofosbuvir/velpatasvir alone versus in combination with ribavirin in cirrhotic patients with HCV. **Methods:** This randomized controlled trial was conducted at the Department of Medicine, CMH Kharian. A total of 120 patients with chronic HCV-related cirrhosis (Child-Pugh B or C) were enrolled and randomly assigned to two treatment groups: Group A (sofosbuvir/velpatasvir) and Group B (sofosbuvir/velpatasvir/ribavirin). Both groups received treatment for 12 weeks, and patients were followed up for 12 weeks post-treatment. **Results:** SVR12 was achieved in 89% of patients in Group A and 92% of patients in Group B. No significant difference was found between the two groups ($p = 0.68$). Treatment failure occurred in 5% of Group A and 6.7% of Group B patients, while relapse rates were 3.3% and 5%, respectively. The incidence of adverse events was higher in Group B (40%) compared to Group A (28.3%), with the most common side effects being nausea, headache, and fatigue. Severe adverse events, including treatment discontinuation, were reported in 3.3% of patients in Group B but were absent in Group A. **Conclusion:** Sofosbuvir/velpatasvir alone is as effective as the combination of sofosbuvir/velpatasvir and ribavirin in achieving SVR12 in cirrhotic patients with HCV. The addition of ribavirin did not significantly improve efficacy but was associated with a higher incidence of adverse events.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is the leading cause of cirrhosis, hepatocellular carcinoma (HCC), and liver transplantation [1]. In Europe, the prevalence of HCV infection is approximately 1.1%, with about 5.6 million affected people [2]. Among the six hepatitis C virus (HCV) genotypes, HCV genotype 1 is responsible for 49% of worldwide HCV infections followed by HCV genotype 3 (18%) [3]. It is estimated that Pakistan stands second in terms of hepatitis C prevalence (4.8%), worldwide [4]. The prevalence of HCV infection further varies within the provinces i.e., 5.46% in Punjab, 2.55% in Sindh, 6.07% in Khyber Pakhtunkhwa, 25.77% in Baluchistan, and 3.37% in federally administrated tribal areas [5]. Genotype 3a is reported to be the most prevalent in Pakistan [6].

Interferon-alpha and Ribavirin have remained the standard HCV treatments for a long period of time with only 50% cure rates [7]. The other limitations such as long therapy duration, self-injections, and substantial toxicity compelled the search for improved alternatives to HCV treatments. With the enhanced insight into the HCV life cycle, new drugs, targeting the viral replication proteins were developed and named direct-acting antivirals (DAAs) [8]. Sofosbuvir (SOF) is an approved HCV non-structural protein 5B (NS5B) inhibitor which is usually administered with other DAAs for HCV infection treatment [9]. Velpatasvir (VEL) is HCV non-structural protein 5A (NS5A) inhibitor having efficacy against all six HCV genotypes [10]. Several studies have reported excellent effectiveness of SOF-VEL alone and with ribavirin for HCV patients of all genotypes.

The effectiveness of HCV treatment by antiviral agents is usually assessed by a sustained virological response (SVR) rate defined as an undetectable viral load (HCV RNA<15IU/ml) 12 weeks off-treatment [11, 12]. In a Japanese study, the overall SVR12 rate was reported as 97% (58/60; 95% CI 88–100%) using sofosbuvir-velpatasvir plus ribavirin treatment regimen for about 24 weeks and 82% (47/57; 95% CI 70–91%) for 12 weeks in the cirrhosis patients [13]. Shah *et al*

reported 89.7% SVR12 using SOF-VEL treatment regimen for 12 weeks in cirrhosis patients [14]. Esteban *et al* compared the efficacy of SOF-VEL (group A) alone VS SOF-VEL (group B) plus ribavirin in genotype 3 HCV infection patients with compensated cirrhosis. The SVR12 was achieved in 91% of patients of group A and 96% of the patients of group B [15].

The rationale of the present study is focused on determining the efficacy of sofosbuvir/ Velpatasvir versus sofosbuvir/ Velpatasvir plus weight-adjusted Ribavirin in Hepatitis C cirrhotic patients at CMH Kharian Gujrat.

OBJECTIVES

The main objective of this study is to compare the efficacy of sofosbuvir/ Velpatasvir versus sofosbuvir/ Velpatasvir plus weight-adjusted Ribavirin in Hepatitis C cirrhotic patients.

MATERIAL AND METHOD

This randomized control trial was conducted at the Department of Medicine, CMH Kharian, during March 2024 to December 2024. Data were collected through the Non-Probability Consecutive Sampling technique.

Sample Size

A total of 120 patients (60 in each group) were enrolled in the study. The sample size was calculated using the WHO sample size calculator, assuming a 10% significance level, 80% power of the test, an anticipated population proportion of 0.897 for one group [14], and an anticipated population proportion of 0.96 for the other group [15].

Inclusion Criteria

- Patients aged between 20 and 80 years.
- Patients diagnosed with chronic Child-Pugh B or Child-Pugh C HCV-related cirrhosis.

Exclusion Criteria

- Patients with a history of hepatocellular carcinoma (HCC) prior to DAA treatment.
- Patients who have undergone liver transplantation.
- Patients co-infected with Hepatitis B virus (HBV).
- Patients co-infected with Human Immunodeficiency Virus (HIV).
- Patients with other liver diseases, such as autoimmune hepatitis, or chronic kidney disease (CKD) stage 4 or 5.

Data Collection

After obtaining approval from the CPSP and the ethical review committee of the hospital, eligible subjects were enrolled in the study. Written informed consent was obtained from all patients. Demographic details, including age, gender, weight, and BMI, were recorded using a pre-designed proforma. Baseline clinical parameters, including hemoglobin levels, International Normalized Ratio (INR), total bilirubin, serum albumin, creatinine, alanine transaminase (ALT), and HCV viral load, were also collected. The degree of liver fibrosis was assessed using shear wave elastography at the start of the study and repeated after 12 weeks. Child-Pugh scores were documented for each patient to assess liver function.

Patients were randomly assigned to one of two treatment groups. Group A consisted of patients receiving a daily dose of 1 tablet of sofosbuvir (400mg) and velpatasvir (100mg) for 12 weeks. Group B received a daily dose of sofosbuvir (400mg), velpatasvir (100mg), and weight-adjusted ribavirin for the same duration. Ribavirin dosing was adjusted based on body weight and renal function. For patients weighing ≥75 kg, ribavirin was administered at 1,200 mg daily, while patients weighing <75 kg received 1,000 mg daily, provided their estimated glomerular filtration rate (eGFR) was ≥50 mL/min/1.73 m². For patients with an eGFR between 30-49 mL/min/1.73 m², ribavirin was administered every other day in doses of 200 mg or 400 mg, irrespective of body weight. Patients were monitored through weekly follow-ups for the 12-week treatment period. The primary efficacy endpoint was the sustained virologic response at 12 weeks (SVR12), defined by the absence of detectable HCV RNA levels as measured by RT-PCR. Secondary efficacy endpoints included treatment failure, relapse, virological failure, treatment withdrawal, and patient mortality. Adverse events (AEs) were categorized based on severity into mild, moderate, and severe categories. Mild AEs included symptoms such as nausea, vomiting, anorexia, headache, and epigastric pain, which did not require hospitalization or treatment interruption. Moderate AEs involved worsening of the Child-Pugh score, derangement of liver function tests, or renal profile. Severe AEs were defined as any event leading to patient death.

Statistical Analysis

The collected data were analyzed using SPSS statistics software version 25.0. Descriptive statistics were used to summarize the quantitative variables, which were expressed as Mean ± Standard Deviation (SD). The Student's t-test or the Mann–Whitney U-test was applied to compare quantitative variables, depending on the data distribution. Qualitative variables were presented as frequencies and percentages, and comparisons were made using the Chi-square test. The primary efficacy endpoints were expressed as percentages, and a p-value of <0.05 was considered statistically significant. This approach ensured that the results were robust and provided reliable insights into the efficacy and safety of the treatment regimens.

RESULTS

Data were collected from 120 patients. The mean age of patients was 55 years, with no significant difference

between the groups (Group A: 55 ± 8 years; Group B: 55 ± 7 years). Hemoglobin levels, serum albumin, total bilirubin, and serum creatinine were similar in both groups, with Group A showing a mean of 12.5 g/dL for hemoglobin, 3.0 g/dL for serum albumin, 1.8 mg/dL for total bilirubin, and 1.2 mg/dL for serum creatinine, closely matched by Group B.

Table 1

Baseline Clinical Parameters

Parameter	Group A (Mean ± SD)	Group B (Mean ± SD)
Age (years)	55 ± 8	55 ± 7
Hemoglobin (g/dL)	12.5 ± 1.2	12.5 ± 1.3
Serum Albumin (g/dL)	3.0 ± 0.6	3.0 ± 0.5
Total Bilirubin (mg/dL)	1.8 ± 0.4	1.7 ± 0.3
Serum Creatinine (mg/dL)	1.2 ± 0.3	1.2 ± 0.4
Gender (Male, %)	36 (60%)	36 (60%)
BMI (Mean ± SD)	26.4 ± 4.1	26.3 ± 3.9
Child-Pugh Score (Mean ± SD)	7.5 ± 1.1	7.6 ± 1.0

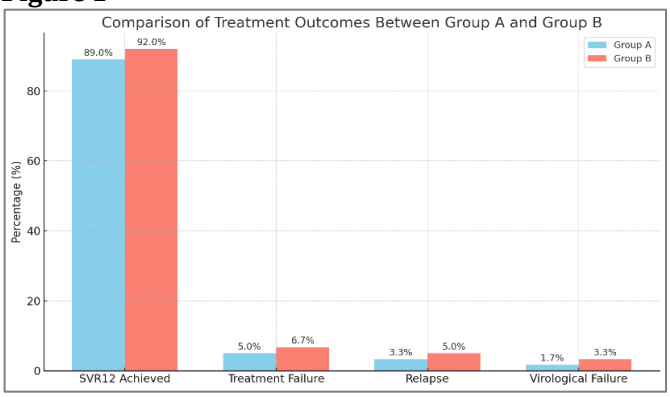
Group A (sofosbuvir/velpatasvir) achieved a 89% sustained virologic response at 12 weeks (SVR12), while Group B (sofosbuvir/velpatasvir/ribavirin) had an SVR12 rate of 92%, with no significant difference between the groups (p = 0.68). Treatment failure was observed in 5% of patients in Group A and 6.7% in Group B (p = 0.72), while relapse occurred in 3.3% of Group A and 5% of Group B patients (p = 0.85). Virological failure was slightly more frequent in Group B (3.3%) compared to Group A (1.7%), but this difference was also not statistically significant (p = 0.74).

Table 2

Efficacy Endpoints

Group	SVR12 Achieved (%)	SVR12 Achieved (N)	p-value
Sofosbuvir/Velpatasvir (Group A)	89%	53	0.68
Sofosbuvir/Velpatasvir/ Ribavirin (Group B)	92%	55	
Treatment Failure	5%	6.7%	0.72
Relapse	3.3%	5%	0.85
Virological Failure	1.7%	3.3%	0.74

Figure 1



The most common mild AEs were nausea (15% in Group A, 20% in Group B), headache (10% in Group A, 13% in Group B), and fatigue (8% in Group A, 12% in Group B), with no significant differences between the groups (p = 0.72, p = 0.72, p = 0.73, respectively). Anorexia was reported in 6.7% of Group A and 8.3% of Group B, also with no significant difference (p = 0.85). However, a significant difference was observed in the incidence of worsening liver function, which occurred in 6.7% of patients in Group B but in none of the patients in Group A (p = 0.04). Renal profile derangement was seen in 5% of patients in Group B but not in Group A (p = 0.06).

Table 3

Treatment-Related Adverse Events

Adverse Event	Group A (N = 60)	Group B (N = 60)	p-value
Nausea	9 (15%)	12 (20%)	0.72
Headache	6 (10%)	8 (13%)	0.72
Fatigue	5 (8%)	7 (12%)	0.73
Anorexia	4 (6.7%)	5 (8.3%)	0.85
Worsening Liver Function	0 (0%)	4 (6.7%)	0.04
Renal Profile Derangement	0 (0%)	3 (5%)	0.06

The sustained virologic response at 12 weeks (SVR12) was achieved in 89% of patients in Group A (sofosbuvir/velpatasvir) and 92 in Group B (sofosbuvir/velpatasvir/ribavirin), with no significant difference between the groups (p = 0.68). Treatment failure occurred in 5% of Group A and 6.7% of Group B patients (p = 0.72), while relapse rates were 3.3% in Group A and 5% in Group B (p = 0.85). Virological failure was slightly higher in Group B (3.3%) compared to Group A (1.7%), but this difference was not statistically significant (p = 0.74). Mortality occurred in 3.3% of patients in Group B, whereas no mortality was observed in Group A (p = 0.15).

Table 4

Follow-up Clinical Outcomes at Week 12

Outcome	Group A (%)	Group B (%)	p-value
Sustained Virologic Response (SVR12)	89	92	0.68
Treatment Failure	5%	6.7%	0.72
Relapse	3.3%	5%	0.85
Virological Failure	1.7%	3.3%	0.74
Mortality (Death)	0%	3.3%	0.15

DISCUSSION

This randomized controlled trial aimed to compare the efficacy and safety of a combination of sofosbuvir and velpatasvir with and without ribavirin in cirrhotic patients with chronic Hepatitis C. The study validated that both the treatment options provided equivalent SVR12 rates in maintaining viral suppression since the results between groups showed no meaningful distinctions. The combination therapy yielded SVR12 achievement rates that were equal in both Groups A and B at 89% and 92% respectively, which disproves the clinical value of ribavirin addition to

sofosbuvir/velpatasvir for this patient group [14]. The observed data matches earlier research regarding ribavirin in DAA-based regimens which demonstrates poor additional benefit from ribavirin treatment in patients who do not need it. The patient outcomes in terms of treatment failure and relapse and virological failure matched between both treatment protocols. The total rate of treatment failure reached 5% in Group A and 6.7% in Group B and their corresponding relapse rates were 3.3% in Group A and 5% in Group B. Clinical trials of sofosbuvir/velpatasvir demonstrated high efficacy in treating chronic Hepatitis C including cirrhotic patients as confirmed by these research findings [15]. Laboratory data reveal ribavirin may not be needed for reaching optimal treatment results among these patients.

Results from the two groups showed comparable safety behavior but Group B led to slightly more mild and moderate adverse event reports [16]. UĜÔO/velpatasvir/ribavirin therapy produced adverse effects of nausea together with fatigue and headache as ribavirin treatment typically creates these complications. Research confirms that ribavirin tends to enhance side effects among cirrhotic patients since they already face challenges from both liver dysfunction and renal impairment [17]. The therapeutic addition of ribavirin to this regimen proved ineffective at enhancing treatment results thus indicating that the dual sofosbuvir and velpatasvir drugs already achieve satisfactory virologic suppression rates in cirrhotic patients [18]. The observation benefits clinical practice since it creates a simple treatment plan and lessens the probability of adverse effects leading to medication breaks or stopping the treatment. The streamlined treatment approach improves patient adherence because it simplifies care for people who currently handle the various challenges of cirrhosis with its related medical problems [19].

Studies have demonstrated that ribavirin addition to DAA therapy can enhance SVR rates mainly for those with severe liver disease or high viral titers yet other research indicates that ribavirin lacks significant impact in the treatment of compensated cirrhosis patients [20]. The combination of sofosbuvir and velpatasvir without ribavirin shows effectiveness as well as tolerability in cirrhotic patients with Hepatitis C according to the findings of our study which builds on existing evidence in this field. The study contains various essential limitations that need recognition. The research took place at one center while its participant number remained low. A larger trial conducted across multiple centers would be essential for validating these study results throughout a wider patient demographic. The 12-week follow-up duration might not establish conclusive measurements of liver function improvement together with hepatocellular carcinoma development risks in cirrhotic patients. Additional assessment with longer follow-up intervals will help determine the long-term outcome advantages of using sofosbuvir/velpatasvir treatment over sofosbuvir/velpatasvir/ribavirin therapy.

CONCLUSIONS

It is concluded that both the combination of sofosbuvir and velpatasvir alone and the combination of sofosbuvir/velpatasvir with ribavirin are highly effective in achieving sustained virologic response at 12 weeks (SVR12) in cirrhotic patients with chronic Hepatitis C. However, no significant difference in efficacy was observed between the two regimens, suggesting that the addition of ribavirin does not provide a substantial advantage in terms of treatment outcomes.

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