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ORIGINAL ARTICLE

EVALUATION OF EFFECTIVENESS AND SAFETY OF SOFOSBUVIR AND RIBAVIRIN COMBINATION IN ACHIEVING EARLY VIROLOGICAL RESPONSE IN CHRONIC HCV GENOTYPE 3 TREATMENT NAÏVE PATIENTS: A PROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Chronic HCV infections pose a greater public health challenge globally, especially effecting resource-limited countries like Pakistan due to its association with rapid progression to fibrosis and hepatocellular carcinoma and spreading at a higher rate. Managing chronic HCV GT3 in low/Middle income regions remains a significant hurdle and thus requires further research. The goal of this study was to evaluate effectiveness and safety of the 4-week Sofosbuvir and Ribavirin combined treatment plan in subjects infected with HCV genotype 3 and no prior treatment between June 2021 and June 2022 at Peshawar Institute of Medical Sciences Hayatabad Peshawar.

Materials & Methods: In our study adult patients (14–75 years) with PCR-confirmed HCV genotype 3, no ultrasound evidence of cirrhosis (Child-Pugh Class A) and no prior antiviral therapy were selected. Demographic, clinical and laboratory data was collected. HCV RNA quantification along with genotyping was conducted before starting the therapy. Patients received Sofosbuvir (400 mg once daily) and Ribavirin (1000 mg/day if <75 kg, 1200 mg/day if ≥75 kg) for 4 weeks. We defined Rapid Virological Response (RVR) as undetectable Hepatitis C Virus RNA (<15 IU/mL) at 4 weeks post treatment. We also recorded some mild and self-limiting adverse effects. Data analysis was done using SPSS v25. We also used Chi-square tests for associations ($p<0.05$= significant).

Results: Out of all the 230 patients enrolled, 228 completed the study (mean age 40.02 ± 13.09 years; 52.6% male, 47.4% female).2 were lost to follow-up. The mean HCV RNA load was $1.95 \times 10^6 \pm 1.2 \times 10^6$ IU/ml. Rapid Virological Response (RVR) was achieved in 222 subjects (97.4%) with not much difference by gender ($p = 0.150$) or age group ($p = 0.312$). Mild adverse events included headache (15.3%), fatigue (13.6%), myalgia (10.1%), and weakness (8.7%) and no treatment discontinuations occurred.

Conclusion: The Sofosbuvir–Ribavirin regimen achieved a high RVR rate and excellent tolerability in individuals with HCV-GT3 and treatment naïve thus making it a cost effective and practical option for resource-limited settings.

KEY WORDS: Antiviral Drugs; Genotype; Chronic Hepatitis C; Ribavirin; Sofosbuvir; Treatment Outcome; Pakistan

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INTRODUCTION

Chronic Hepatitis C virus (HCV) infection continues to be a significant health challenge worldwide, impacting an estimated 64-103 million people, with a particularly high burden in low and middle-income countries.[1,2] Of the many strains of HCV, GT3 is the second most prevalent strain globally, significantly contributing to the overall incidence of chronic liver diseases especially in regions like Central Asia, South Asia and parts of the East Asia. In fact, ap-

proximately 25%-30% of all HCV cases worldwide are due to GT3 infections.[3]

In Pakistan the situation is particularly alarming with approximately 6.7% of the population being affected by Hepatitis C, with Genotype 3 accounting for around 79% of these cases. This makes HCV-GT3 the dominant strain in the country amplifying the public health crisis.[4] Genotype 3 has tendency to cause faster progression to serious liver diseases such as cirrhosis, fibrosis and carcinomas when compared to other genotypes.[3, 5, 6] Here it is more concerning as access to high quality healthcare and diagnostic tools is still limited especially in under-served and resource constrained areas of Pakistan, where the healthcare system is underdeveloped.[2] This makes managing chronic HCV genotype 3 in low and middle-income countries a significant challenge, thus underlining the need for more research into affordable and accessible treatments.[7]

Historically, HCV treatment relied heavily on interferon-based therapies which even though available, were less effective and came with severe side effects thus making it difficult for patients to stick to the regimen and leading to treatment failures.[8] The emergence of direct-acting antiviral (DAA) therapies has been a game changer in the treatment of HCV. Sofosbuvir (SOF), a nucleotide analog which is designed to inhibit the HCV NS5B polymerase enzyme when combined with Ribavirin (RBV) has shown remarkable effectiveness by reducing the replication of the virus.[1,] This combination therapy has not only led to higher cure rates but also caused fewer side effects compared to older treatments thus offering new hope to HCV patients around the world.[4]

Despite the widespread use of Sofosbuvir and Ribavirin, their effectiveness has not been thoroughly studied in Pakistan especially low resource settings where HCV is most common Considering the widespread presence of genotype 3 in Pakistan, the understanding of how well this combination therapy works and how well patients tolerate it in such settings is important. The success of a 4-week Sofosbuvir and Ribavirin treatment course in achieving a Rapid Virological Response (RVR) which is an early key marker of long-term treatment success. It could offer valuable insights into how to improve HCV care in the country.[2] Achieving RVR is defined as the absence of detectable HCV RNA within the initial four weeks of treatment[9]. RVR is a strong predictor of SVR, which is measured at 12 or 24 weeks and considered as a measure of long-term success.[1, 10]

The goal of this study was to evaluate the effectiveness and safety of the 4-week Sofosbuvir and Ribavirin combined regimen in patients infected with HCV-GT3 and treatment naïve between June 2021-June 2022 at Peshawar Institute of Medical Sciences Hayatabad Peshawar. The findings from this study will help address the significant knowledge gap regarding the practical application of Sofosbuvir and Ribavirin combination therapy for HCV-GT3 in Pakistan.

MATERIALS AND METHODS

Our prospective observational study was carried out at Peshawar Institute of Medical Sciences Hayatabad Peshawar from June 2021 to June 2022. We used WHO sample size calculator for calculating a sufficient sample size for a single proportion, with an anticipated RVR rate of 95% based on previous studies, a 95% confidence interval and a 3% error margin. This yielded a minimum recommended sample size of 203 participants. We recruited 230 patients to adjust for loss to follow-up. Ethical approval was obtained from the institutional review board before patient enrollment. All participants gave their written informed consent. The criteria for inclusion in the study were as follow: participants had to have a PCR-confirmed diagnosis of HCV genotype 3 infection, be between the ages of 14 and 75 years and show no ultrasound evidence of cirrhosis (Child-Pugh Score A). Additionally, only treatment navïe patients were considered for inclusion. Conversely, the exclusion criteria encompassed individuals with cirrhosis (Child-Pugh Score B or worse), co-infections with hepatitis B or HIV, past HCV treatment or those <14 years old.

Patients were administered Sofosbuvir (400 mg/day) and Ribavirin on weight-based (1000mg in divided doses for weight < 75kg and 1200mgfor weight >75kg) for a duration of 4-weeks. Treatment adherence was monitored at scheduled follow-ups.

Baseline demographic, clinical and laboratory data of patients was recorded. HCV RNA quantification and genotyping were performed prior to initiating therapy. Similarly, follow-up PCR testing was conducted at 4 weeks along and data was analyzed via SPSS version 25. Continuous variables were presented as means ± standard deviation (SD) or medians with interquartile ranges (IQR) as applicable. We expressed categorical variables as frequencies and percentages. Similarly, associations among categorical variables and RVR were evaluated using the chi-square test with a p-value <0.05 (statistically significant)

RESULTS

In this study 230 patients were enrolled consisting of 120 males (52.2%) and 110 females (47.8%), with mean age of 40.02 ± 13.09 years (range: 14–75 years). The majority (81.7%, n=188) were under 50 years of age. Two participants were lost during follow-up. All participants had no treatment before and no ultrasound confirmation of cirrhosis (Child-Pugh Class A).

The age distribution of the cohort is detailed in (Table 1). Mean age was 40.02 ± 13.09 years, with the majority of patients (81.7%) being under 50 years of age.

Table 1: Age distribution

Age group (years)	Frequency (n)	Percentage (%)
14–19	18	7.9
20–29	55	24.1
30–39	62	27.2
40–49	53	23.2
50–59	28	12.3
≥60	12	5.3
Total	228	100.0
Mean ± SD	40.02 ± 13.09	

The gender distribution is shown in (Table 2). Male to female ratio was about 1.1:1.

Table 2: Gender distribution

Gender	Frequency (n)	Percentage (%)
Male	120	52.6
Female	108	47.4
Total	228	100.0

Baseline laboratory parameters, measured prior to treatment initiation, are summarized in (Table 3).

Table 3: Baseline Laboratory Parameters

Metrics	Mean ± SD	Min	Max
Hb (g/dL)	13.6 ± 1.4	10.5	16.8
Total Leukocyte Count ($\times 10^9$/L)	6.2 ± 1.5	3.8	10.4
Platelet Count ($\times 10^9$/L)	245 ± 55	150	390
Serum Bilirubin (mg/dL)	0.9 ± 0.3	0.4	1.8
AST (U/L)	45 ± 18	22	102
ALT (U/L)	78 ± 30	28	210
S-Alb (g/dL)	4.1 ± 0.4	3.3	4.9
INR	1.05 ± 0.08	0.92	1.2

Distribution of baseline viral load values is shown in (Table 4).

Table 4: Baseline HCV RNA Load

Viral Load (IU/mL)	Mean	SD	Min	Max
HCV RNA load	1,950,000	1,200,000	150,000	8,500,000

Comparison of RVR rates by gender and age group is shown in (Tables 5 and 6).

Table 5: Rapid Virological Response (RVR)

Gender	RVR Achieved n (%)	RVR Not Achieved n (%)	p-value
Male	115 (96.0)	5 (4.0)	0.150
Female	107 (97.3)	1 (2.7)	

Age group	RVR Achieved n (%)	RVR Not Achieved n (%)	p-value
<50 years	184 (97.9)	4 (2.1)	0.312
≥50 years	38 (90.5)	2 (9.5)	

No severe adverse events were recorded. The most common mild side effect are listed in (Table7). All were self-limiting and did not require treatment discontinuation.

Table 7: Adverse Events

Adverse Event	Frequency (n)	Percentage (%)
Headache	35	15.3
Fatigue	31	13.6
Myalgia	23	10.1
Weakness	20	8.7

DISCUSSION

The findings from this study highlights the impressive effectiveness of the 4-week Sofosbuvir and Ribavirin blended therapy for treatment naïve patients with chronic HCV-GT3 infection. An outstanding 97.4% of participants achieved RVR at four weeks, with 222 patients out of 228 having undetectable HCV RNA. This outcome aligns with the high RVR rates observed in similar studies, such as the one conducted by Mei YY et al., which further supports the efficacy of Sofosbuvir and Ribavirin for genotype 3 patients.[9] The finding that RVR rates were independent of gender and age suggests that this combination therapy works equally well across different demographic groups similar to the studies such as Hideyuki Tamai et al. and Sirinawasatien A et al.[11,12] Additionally, Sofosbuvir-based treatments have shown remarkable effectiveness in patients with HCV-GT3, particularly in regions with greater genotype prevalence such as Khyber Pakhtunkhwa province.[2]

Previous research has highlighted that genotype 3 patients, particularly those with advanced liver morbidities or cirrhosis tend to have higher relapse rates after treatment.[13] However, in our study 97.4% of patients achieved RVR, indicating that Sofosbuvir and Ribavirin can provide an effective treatment option even in resource constrained areas like Khyber Pakhtunkhwa province, where access to newer DAAs

such as Sofosbuvir and Velpatasvir, may be limited.[14] The success of four -week therapy of Sofosbuvir and Ribavirin in achieving RVR which is a crucial early marker of long-term treatment success, provides valuable insights for improving HCV management in rural areas of Pakistan.

In terms of safety the treatment demonstrated a favorable safety profile with only mild adverse effects reported, including headache (15.3%), fatigue (13.6%), myalgia (10.1%), and weakness (8.7%). These side effects are consistent with the well-established safety profile of Sofosbuvir and Ribavirin.[2, 10] Furthermore no severe unfavorable event or treatment discontinuation was reported due to side effects, which is important when considering the feasibility of implementing such treatments in resource constrained settings. The combination of high efficacy and good tolerability suggests that Sofosbuvir and Ribavirin can be considered a frontline treatment for chronic HCV genotype 3 particularly in regions like Khyber Pakhtunkhwa province.

Despite the promising results, the study identified that 2.6% of patients did not achieve RVR. This highlights the complexity of HCV treatment in certain populations, as non-response to treatment can be influenced by factors such as advanced liver disease, genetic variation in HCV strains, and comorbidities.[15] While the overall treatment success rate was high, this small proportion of non-responders suggests the need for personalized treatment strategies and closer monitoring for these patients. Further research is needed to understand the underlying factors contributing to treatment failure in this subset, which could inform adjustments to treatment duration or combination regimens.

Although the outcomes of our study are promising, the short duration of treatment (4 weeks) means that the long-term sustainability of these outcomes, specifically the SVR rates is yet to be determined. SVR, which is defined as undetectable HCV RNA 12- and 24-weeks post-treatment, remains a gold standard for determining long term treatment success and cure.[10] Future studies should follow up with participants beyond the 4-week period to determine whether the high RVR rates observed in this study translate into lasting viral suppression and cure. Given the concerns about relapse and reinfection in high transmission regions like Pakistan, investigating the durability of response will be crucial for establishing the long-term effectiveness of Sofosbuvir and Ribavirin in the local context.

Limitations: Even though the current study demonstrates the effectiveness and safety of Sofosbuvir and Ribavirin in KPK province, Pakistan, there are limitations that need to be addressed. One such limitation is the lack of a control group, which means that the results cannot be directly compared with other treatment regimens such as newer Sofosbuvir based combinations or interferon free treatments. Notably as our study focus was primarily on treatment naïve patients, it might be beneficial to examine the efficacy of this regimen in patients who have previously failed other treatments or have advanced liver disease.

CONCLUSION

In conclusion a 4-week regimen of Sofosbuvir plus weight-based Ribavirin produced a high RVR rate (97.4%) in treatment-naïve, non-cirrhotic genotype 3 patients from KPK province, Pakistan. Baseline viral load and laboratory parameters were within ranges compatible with good treatment response and neither gender nor age significantly influenced RVR. The regimen was well tolerated with only mild self-limiting adverse events and no treatment discontinuations, making it a viable and cost-effective option for resource-limited settings.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	TMK, NAK
Acquisition, Analysis or Interpretation of Data:	TMK, NAK, SAK, MTM, MR
Manuscript Writing & Approval:	TMK, NAK, SAK, MTM, MR

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.