ORIGINAL ARTICLE

ROLE OF RAPID VIROLOGICAL RESPONSE IN PREDICTING THE ADVERSE EFFECTS OF SOFOSBUVIR AND RIBAVIRIN THERAPY IN CHRONIC HEPATITIS C PATIENTS

MUHAMMAD IRFAN,[1] NAVEED ASLAM,[1] AHSEN NAQVI,[2] GHULAM MUSTAFA AFTAB[3]
BARUN KUMAR SHAH,[4] JAMSHED LATIF,[1] MUHAMMAD ARIF NADEEM,[5] AFTAB MOHSIN[6]
[1]Department of Medicine, Gujranwala Medical College, Gujranwala, Pakistan. [2]Naas General Hospital, Ireland [3]CMH Medical College, [4]KEMC, [5]SIMS / Services Hospital Lahore, [6]Liver Clinic, Lahore and Gujranwala Medical College, Gujranwala, Pakistan

ABSTRACT

Objective: *To determine the role of Rapid Virological Response in predicting the adverse effects of Sofosbuvir and Ribavirin Therapy in chronic Hepatitis C patients.*

Study Design: *Prospective cohort study.*

Place and Duration of Study: *Liver clinic, 250 Shadman, Lahore, from January 2015 to December 2015.*

Methodology: *Patients with chronic hepatitis C were treated with Sofosbuvir plus ribavirin for 24 weeks. The response to therapy was checked at 4 and 24 weeks of treatment, that is known as Rapid Virological Response (RVR) and End Treatment Response (ETR) respectively. The adverse effects of therapy were noted at every 4 weekly visit for whole 24 weeks of therapy. Baseline population characteristics were noted. For anaemia, new onset or worsening in existing anaemia was considered significant while emergence of fatigue, headache, cough, insomnia and pruritus during therapy was also noted. The statistical relation of lack of RVR with adverse effects of therapy was checked using SPSS version 15.*

Results: *Out of a total of 100 patients, 52% were women and 48% were men. The age of the patients ranges from 22 to 70 years with a mean of 45.68 ± 10.71 years. RVR was 91% (910ut of 100) while ETR was 95% (95 out of 100). 38% patients have anemia at baseline while 62% have no anemia. During therapy, 66% patients have new onset or worsening of anemia. Other adverse effects that developed during therapy were fatigue (56%), headache (39%), cough (23%), insomnia (14%) & pruritus (5%). Lack of RVR had statistically significant relation with fatigue (p = 0.037), headache (p = 0.002), cough (p = 0.000) and insomnia (p = 0.021).*

Conclusion: *The response of chronic Hepatitis C patients to Sofosbuvir plus Ribavirin Therapy is remarkable in Pakistani population. Lack of RVR at week 4 of therapy predicts the occurrence of majority of adverse effects of treatment during whole 24 weeks of therapy.*

Key words: *Hepatitis C. Sofosbuvir. Ribavirin. Adverse Effects, Rapid Virological response.*

INTRODUCTION

Hepatitis C Virus (HCV) is a major health issue in Pakistan[1], affecting about 3-13% of its population.[2] Sofosbuvir plus ribavirin is an excellent treatment option[3], with higher response rate and low adverse effects as compared to previous popular interferon therapies.[4] The duration of sofosbuvir plus ribavirin therapy is 24 weeks[5] and the response of treatment is checked using real time HCV-RNA polymerase chain reaction (PCR) test.[6] Rapid Virological Response (RVR) is defined as negative HCV-RNA PCR test at week 4 of treatment.[7] The most common adverse effects (≥ 20%) observed with sofosbuvir plus ribavirin therapy are fatigue and headache.[8] Other adverse effects include anaemia, insomnia, pruritus & dry cough.[9] If patient is not getting cure by some treatment, then why he or she should suffer the adverse effects of that therapy. This question convinced the authors to look for any relation between the response of treatment to its adverse effects.

The objective of this study was to determine the role of rapid virological response in predicting the

adverse effects of sofosbuvir and ribavirin therapy in chronic hepatitis C patients.

METHODOLOGY

This was a prospective cohort study carried out at Liver Clinic, 250 Shadman, Lahore, Pakistan, from January 2015 to December 2015. A total 100 patient of chronic hepatitis C aged 5 years and above with positive HCV RNA were enrolled. The exclusion criteria was patients with decompensated liver disease and child pug score >12, pregnancy, HIV and/or HBV co-infection and renal dysfunction with creatinine clearance <50 mL /minute.

The enrolled patients were treated with a combination of sofosbuvir and ribavirin for 24 weeks. Sofosbuvir was given in a dose of 400mg daily, while ribavirin was given 1000 mg in divided doses for patients weighing less than 70 kg and 1200 mg for those weighing 70 kg and above.[3]

Adverse effects of sofosbuvir plus ribavirin therapy like anemia, fatigue, headache, cough, insomnia & pruritus were noted at every 4 weekly visit for whole 24 weeks of therapy. Baseline population characteristics were noted. For anemia, new onset or worsening in existing anemia was considered significant while emergence of fatigue, headache, cough, insomnia and pruritus during therapy was also noted. Biochemical and hematological testing was performed every 4 weeks for whole 24 week therapy, and serum HCV-RNA testing was performed at week 4 and at end of treatment to see for RVR & ETR respectively. During data interpretation, the anemia was defined as hemoglobin (Hb) level of less than 13.5 g/dl for males and less than 12g/dl for females.[10]

The descriptive analysis of the collected data was done using SPSS version 15. Gender, age groups, RVR, ETR, anemia, fatigue, headache, cough, insomnia & pruritus were the qualitative variables, while age was the only quantitative variables. Investigational data was interpreted in negative or positive values. For quantitative variables, means and standard deviations were calculated and for qualitative variables, frequencies and percentages were computed. Chi-square test was applied to find association of factors at 5% level of significance. Odd ratio with 95% confidence interval (CI) was also calculated for each association.

RESULTS

A total of 100 cases were enrolled and treated with sofosbuvir and ribavirin for 24 weeks. Forty eight cases (48%) were men and 52 (52%) women. Mean age of patients was 45.68 ± 10.71 years. Out of the 100 cases, RVR was seen in 91 (91%) cases while ETR in 95 (95%) cases. 38% patients had anemia at baseline while 62% had no anemia. During therapy, 66% patients had new onset or worsening of anemia. Other adverse effects that developed during therapy were fatigue (56%), headache (39%), cough (23%), insomnia (14%) & pruritus (5%). All these adverse effects were of mild intensity and easily manageable. No serious adverse event occurred and none of these patients was dropped out of the study (Table 1).

Two groups of patients (who achieved RVR versus who did not achieve RVR) were compared in term of adverse events including anemia, fatigue, headache, cough, insomnia and pruritus. Among patients who did not achieve RVR, 88.9% (8 out of 9) suffered fatigue, 88.9% (8 out of 9) headache, 88.9% (8 out of 9) cough & 44.4% (4 out of 9) suffered insomnia. Their associations with lack of RVR were statistically significant with p-values of 0.037, 0.002, 0.000 & 0.021 respectively. However, the association of lack of RVR with anemia & pruritus was statistically not significant (Table 2).

DISCUSSION

The known adverse effects of sofosbuvir plus ribavirin therapy are headache, fatigue, pruritus, insomnia, cough and anemia with a frequency of 30%, 30%, 27%, 11%, 10% & 6% respectively.[11] However in our study, the most common adverse effect was anemia seen in 66% of the patients & the pruritus being less common (5%). This may point the need of larger studies to see the diversity of adverse effects in our population.

International data show that treatment discontinuation because of adverse events was only 1% among patients receiving sofosbuvir-ribavirin therapy because of malaise and headache.[11] However in our study, patients follow up was 100% and all adverse effects were of mild intensity & easily manageable.

Available data are lacking to show any early prediction of adverse effects by using available tools; however our study points that lack of RVR make the patient prone to majority of adverse effects of the treatment like fatigue, headache, cough & insomnia. In contrast, effectiveness of treatment guaranteed for less adverse effects as well. The hypothetical possible reasons for this difference may be bias, drug pharmacokinetics, patient's genetic differences and preexisting co-morbidities. Further studies should be performed to validate this benefit of RVR testing in hepatitis C patients getting sofosbuvir-ribavirin Therapy. It is also suggested that for our people recommendations should be reconsidered by local authorities on the basis of local data. Further studies may facilitate to solve the issue.

CONCLUSION

The adverse effects of sofosbuvir plus ribavirin in our population were of mild intensity and easily manageable so that treatment compliance was 100%. Anemia was the most common adverse effect, followed by fatigue, headache, cough, insomnia and pruritus in the

studied patients. Lack of RVR predicts the occurrence of majority of adverse effects of treatment during whole 24 weeks of therapy.

Table 1: *Frequency distribution of qualitative variables (n = 100).*

Factors	Category	Frequency	Percentage
Gender	Male Female	48 52	48.0 52.0
Age	<45 ≥45	40 60	40.0 60.0
RVR	Achieved Not-achieved	91 09	91.0 09.0
ETR	Achieved Not-achieved	95 05	95.0 05.0
Anemia (new onset + worsening)	Yes No	66 34	66.0 34.0
Fatigue	Yes No	56 44	56.0 44.0
Headache	Yes No	39 61	39.0 61.0
Cough	Yes No	23 77	23.0 77.0
Insomnia	Yes No	14 86	14.0 86.0
Pruritis	Yes No	5 95	5.0 95.0

RVR = Rapid Virological response; ETR= End Treatment Response

Table 2: *Statistical correlation between Adverse Effects of Sofosbuvir plus Ribavirin Therapy & RVR (achieved/ not-achieved) (n = 100).*

Adverse Effects/Categories		RVR		p-value	Odd ratio with 95% Confidence interval
		Achieved	Not-achieved		
Anemia:	Yes No	58 (63.7%) 33 (36.3%)	8 (88.9%) 1 (11.1%)	0.161	0.220 (0.026-1.835)
Fatigue:	Yes No	48 (52.7%) 43 (47.3%)	8 (88.9%) 1 (11.1%)	0.037	0.410 (0.017-1.162)
Headache:	Yes No	31 (34.1%) 60 (65.9%)	8 (88.9%) 1 (11.1%)	0.002	0.065 (0.008-0.540)
Cough:	Yes No	15 (16.5%) 76 (83.5%)	8 (88.9%) 1 (11.1%)	0.000	0.025 (0.003-0.212)
Insomnia:	Yes No	10 (11.0%) 81 (89.0%)	4 (44.4%) 5 (55.6%)	0.021	0.154 (0.035-0.671)
Pruritus:	Yes No	04 (04.4%) 87 (95.6%)	1 (11.1%) 8 (88.9%)	0.382	0.368 (0.037-3.698)

RVR = Rapid Virological response

Corresponding Author: Muhammad Irfan
Department of Medicine, Gujranwala Medical College, Gujranwala, Pakistan
E-mail address: Irfanmed3@yahoo.com

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