Comparison of sofosbuvir, ribavirin plus peg-interferon-α treatment with sofosbuvir plus ribavirin alone in patients with chronic Hepatitis C

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ABSTRACT

Objective: To compare the efficacy of weekly Peg-interferon-α, weight based ribavirin and sofosbuvir daily for 12 weeks with weight based ribavirin and sofosbuvir daily for 24 weeks in patients with genotype 3a chronic hepatitis C patients.
Study Design: Cross-sectional analytical comparative study
Place and Duration: Department of Medicine, Aziz Bhatti Shaheed Teaching Hospital Gujrat from November 2015 to July 2017
Methodology: Patients with chronic hepatitis C genotype 3 infection were divided in two equal groups. Group A included patients treated with Peg-interferon-α weekly, weight based ribavirin and sofosbuvir daily for 12 weeks and group B included patients treated with weight-based ribavirin and sofosbuvir daily for 24 weeks.
Results: Each group contained 107(N) patients. Mean age in group A was 42.22+10.66 years compared to 49.66+10.51 years in group B. Early virological response (EVR) was achieved by 98.13% patients in group A compared to 97.2% in group B. End treatment response (ETR) rates were similar in both groups as EVR rates. Sustained virological response at 24 weeks (SVR_{24}) was achieved by 94% patients in group A compared to 90% in group B. Binary logistic regression analysis showed no association of treatment history and presence of cirrhosis with either of EVR, ETR or SVR_{24} ($p>0.05$). Significant difference in treatment response with either regimen was not noted.
Conclusion: Dual and triple therapy regimens are equally effective in treating chronic hepatitis C genotype 3 patients.
Keywords: Peg-interferon-α, Sofosbuvir, HCV, Genotype 3, Hepatitis C, Ribavirin,

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INTRODUCTION

Chronic Hepatitis C (CHC) is a major health concern affecting 170 million people globally[1]. Pakistan is worst affected with chronic hepatitis C virus and the has one of highest prevalence of hepatitis C infection approaching 6.7%[2]. One recent study conducted in Pakistan demonstrated the prevalence of 4.9%[3]. Among patients infected with chronic hepatitis C virus (HCV), genotype 3a and 2a are two most prevalent genotypes affecting almost 90% patients[2,3]. Multiple studies have identified subtype 3a as the commonest HCV variant in Pakistan[3-5].

Sofosbuvir is one of directly acting antivirals (DAAs); inhibitor of NS5B polymerase in HCV virus and got approval in December 2013 from United States Food and Drug Administration (FDA) for treatment of chronic hepatitis C[6]. According to European Association for the Study of the Liver (EASL) 2015 guidelines for treatment of hepatitis C patients, patients infected with genotype 3 can be treated with either weekly Peglated interferon-α, weight based ribavirin and sofosbuvir daily for period of 12 weeks or ribavirin (weight based) and sofosbuvir daily for 24 weeks or sofosbuvir and daclatasvir daily for period of 12 weeks[7]. However latest EASL guidelines excluded all these regimens for treatment of hepatitis C genotype 3[8].

One recent study conducted in Egypt comparing both regimens found out that both regimens are equally effective in treating chronic hepatitis C patients[9]. Furthermore the comparative efficacy of both regimens was found to be having similar

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efficacy in other studies[10,11].

Decreased prices of sofosbuvir in Pakistan with arrival of generic drugs has led to easily availability to patients for treatment[12] although a few DAAs are available for treatment. Pakistan is among the top countries starting DAAs for treatment of chronic hepatitis C in 2016[13]. Interferon free regimens provide a better quality of life for the patients. There are no studies in Pakistan which have been done so far comparing effectiveness of different sofosbuvir based regimens with or without interferons in patients with genotype 3 of CHC.

The objective of current study was to compare the efficacy of weekly Peg-interferon-α, weight based ribavirin and sofosbuvir daily for 12 weeks with weight based ribavirin and sofosbuvir daily for 24 weeks in patients with genotype 3 chronic hepatitis C patients.

METHODOLOGY

This cross-sectional analytical comparative study was done in Aziz Bhatti Shaheed Teaching Hospital Gujrat from 1st November 2015 to 31st July 2017. Patient was selected using non-probability purposive sampling. Adults with age >18 years and BMI >18Kg/m^2 were enrolled in two equal and comparable groups with respect to age, treatment history, presence of cirrhosis and Child Pugh Score.

Patients having decompensated cirrhosis or co-infection with chronic hepatitis B or HIV or patients having history of a medical condition associated with chronic liver disease were excluded from study after relevant investigations. Patients having either compensated cirrhotic (Child A & B) or non-cirrhotic; treatment naive and treatment experienced patients with chronic hepatitis C genotype 3 were included in study after approval of ethical committee of hospital.

Cirrhosis was defined on ultrasound abdomen in patients having mild to severely coarse echotexture of liver and was performed by consultant radiologist (Toshiba Nemio 3). Although Shear Wave Elastography and Fibroscan are recommended investigations for cirrhosis but these modalities were not available in our setup. Patients having treatment experienced with 24 weeks interferon plus ribavirin patients were further classified in two sub-groups. Patients who did not respond were sub-grouped as non-reponders and those who had a positive PCR after achieving sustained virological response were sub-grouped as relapsers. Severity of liver disease in patients with cirrhosis was calculated using Child Pugh Score. Patients with score of 5-6 were considered having Child Class A, 7-9 as Child Class B and 10-15 as Child Class C[14].

Data was collected using a proforma by authors. Age of patient, gender, treatment experience, Child Pugh score and presence of cirrhosis were noted. Patients were given treatment based on preference and enrolled in study after informed consent. Patients were treated according to recommended guidelines of respective time and availability of drugs in our setup. Two groups of patients were made. Group A had patients treated with Peg-interferon-α weekly, weight based ribavirin and sofosbuvir (400 mg) daily for 12 weeks and group B included patients treated with weight based ribavirin and sofosbuvir (400 mg) daily for 24 weeks.

A baseline quantitative PCR for HCV RNA was done and those having values >15ng/ml was considered as positive. To assess the response of treatment at 4th week (Early Virological Response or EVR) and at the end of 12th or 24th week of treatment (End Treatment Response or ETR), a quantitative PCR was done. Sustained virological response (SVR_{24}) at 24 weeks after treatment completion was considered as primary end point. Tolerability of drug and side effects were not noted and patients not receiving full therapy due to side effects or death due to any cause were excluded.

Statistical analysis was done using SPSS version 20.0. Results are expressed as mean±standard deviation (SD) for continuous variables such as age and number (percentage) for categorical data such as gender, cirrhosis and Child Pugh Score. Association of confounding variables like cirrhosis and treatment history on likelihood that patients will achieve EVR, ETR or SVR was determined using binary logistic regression analysis. Both treatment groups were compared for virological response and relative ratio of achieving EVR, ETR and SVR were calculated and p-value of < 0.05 was considered significant.

RESULTS

Total 214 patients were included in the study. They were divided in two equal groups of 107 patients in each. Patients were matched for age, treatment history, presence of cirrhosis and Child Pugh Class. In group A 35(32.7%) were male and 72(67.3%) were female while in group B 33(30.8%) were male while 74(69.2%) were female. Mean age in group A was 42.22+10.66 years while mean age in group B was 49.66+10.51 years. Cirrhosis was present in 30(28.01%) patients in each group out of which 20 (18.7%) were Child Class A and 10 (9.35%) were Class B. Regarding treatment experience, 83 (77.57%) patients had no previous treatment (treatment naïve), 11 (10.28%) were interferon non-responders and 13 (12.15%) were interferon relapsers were included in each group.

In group A, early virological response (EVR) was achieved by 105(98.13%) patients. Patients who failed to achieve EVR included patients who were treatment experienced. One patient was cirrhotic non-responder and other was non-cirrhotic relapser. All 105 (98.13%) patients who achieved EVR also achieved end treatment response (ETR). Eight patients lost to further follow up and data of only 99 patients were obtained for sustained virological response at 24 weeks (SVR_{24}) after end of treatment. Out of these 93 (94%) achieved SVR_{24}. Depicted in Table-I.

Table-I: Treatment Response in Group A (Peg-interferon-α, ribavirin and sofosbuvir for 12 weeks)

Response to Treatment	Treatment History	Cirrhosis				Overall Response %	Total Patients in Group	
		Present		Absent				
		(n)	%	(n)	%		(n)	%
EVR	Treatment Naïve	21	19.63%	62	57.94%	**98.12%**	83	77.57%
	Non-Responders	4	3.74%	6	5.6%		11	10.28%
	Relapsers	4	3.74%	8	7.48%		13	12.15%
	Total	29	27.1%	76	71.02%		107	100%
ETR	Treatment Naïve	21	19.63%	62	57.94%	**98.12%**	83	77.57%
	Non-Responders	4	3.74%	6	5.6%		11	10.28%
	Relapsers	4	3.74%	8	7.48%		13	12.15%
	Total	29	27.1%	76	71.02%		107	100%
SVR_{24}	Treatment Naïve	20	20.2%	57	57.58%	**94.0%**	78	78.78%
	Non-Responders	2	2.02%	5	5.05%		9	9.1%
	Relapsers	2	2.02%	7	7.07%		12	12.12%
	Total	24	24.24%	69	69.7%		99	100%

EVR – Early Virological Response, ETR – End Treatment Response, SVR – Sustained Virological Response

Table II. Treatment Response in Group B (Ribavirin and Sofosbuvir for 24 weeks)

Response to Treatment	Treatment History	Cirrhosis				Overall Response %age	Total Patients in Group	
		Present		Absent				
		(n)	%	(n)	%		(n)	%
EVR	Treatment Naïve	20	18.7%	62	57.94%	**97.2%**	83	77.57%
	Non-Responders	4	3.74%	6	5.6%		11	10.28%
	Relapsers	4	3.74%	8	7.47%		13	12.15%
	Total	29	26.18%	77	71.01%		107	100%
ETR	Treatment Naïve	20	18.7%	62	57.94%	**97.2%**	83	77.57%
	Non-Responders	4	3.74%	6	5.6%		11	10.28%
	Relapsers	4	3.74%	8	7.47%		13	12.15%
	Total	29	26.18%	76	71.01%		107	100%
SVR_{24}	Treatment Naïve	19	18.81%	59	58.42%	**90.0%**	80	79.21%
	Non-Responders	2	1.98%	5	4.95%		10	9.9%
	Relapsers	3	2.97%	3	2.97%		11	10.89%
	Total	24	23.76%	67	66.3%		101	100%

EVR – Early Virological Response, ETR – End Treatment Response, SVR – Sustained Virological Response

In group B, early virological response (EVR) was achieved by 104(97.2%) patients. Patients who failed to achieve EVR included patients who were both treatment naïve and treatment experienced. Two patients was cirrhotic, one treatment naïve and other was non-responder while third patient was non-cirrhotic relapser. All 104 (97.2%) patients who achieved EVR also achieved end treatment response (ETR). Six patients (5.6%) lost to further follow up in this group and data of only 101 (94.4%) patients were obtained for sustained virological response at 24 weeks (SVR_{24}) after end of treatment. Out of these 91 (90.1%) achieved SVR_{24}. Depicted in Table-II.

Binary logistic regression analysis showed no association of treatment history and presence of cirrhosis with either of EVR, ETR or SVR ($p>0.05$). The relative ratio for achieving EVR and ETR with peg-interferon-α, ribavirin and sofosbuvir compared to sofosbuvir plus ribavirin was 1.0096 (CI 95%, 0.9696-1.0524). The relative ratio of achieving SVR in group A in comparison to group B was 1.0588 (CI 95%, 0.9137- 1.2271). No significant difference in treatment response was noted in both groups.

DISCUSSION

This study compared the EVR, ETR and SVR after 24 weeks of ending treatment in patients treated with weekly peg-interferon alpha, daily sofosbuvir plus weight based ribavirin with daily sofosbuvir and weight based ribavirin alone. Patients from both gender were included study was conducted in both cirrhotic and non-cirrhotic patients as well as treatment naïve and treatment experienced patients. EVR, ETR and SVR_{24} in available patients were better achieved in in patients treated with weekly peg-interferon alpha, daily sofosbuvir plus weight based ribavirin as compared to daily sofosbuvir and weight based ribavirin alone. However both treatments were equally effective in treatment of CHC genotype 3 patients without significant association of treatment history and cirrhosis in achieving virological response

Regarding age and gender of patients included in the study group, it shows that CHC is common in young people and is twice more common in females than males. More

seropositivity among females have been attributed to transfusion of blood, sexual contact, dilation and curettage and cesarean section[15]. Thus the pattern of gender involvement is similar to other studies conducted in chronic hepatitis C patients.

In case of patients treated with combination of sofosbuvir, ribavirin and peg-interferon for 12 weeks, Lawitz et al. demonstrated SVR4 (88%), SVR12 (83%) and SVR24 (83%) in treatment experienced patients with genotype 3 when given this regimen[16]. Their results show low rates of SVR as compared to group A of this study. These low rates may be attributed to smaller sample size compared to group A of this study and only inclusion of treatment experienced patients in their study.

When two treatment regimens were compared by Foster et al., they showed better results of 12 weeks sofosbuvir, ribavirin and peg-interferon in genotype 3 CHC patients (SVR12 93%) as compared to 16 weeks daily sofosbuvir and ribavirin (SVR12 71%) and 24 weeks daily sofosbuvir and ribavirin (SVR12 84%)[17]. Their study has similar results to results of this study. However they compared three treatment regimens as compared to two regimens of this study. When comparable regimens are considered, their study validates our results. SVR_{24} is slightly higher in our study in both groups. This slight difference may be attributed to higher number of treatment experienced patients in their study group.

When comparing different treatment regimens of DAAs, Wehmeyer et al. showed that patients treated with sofosbuvir plus ribavirin had SVR12 rates of 69.4% compared to those treated with sofosbuvir, ribavirin and peg-interferon who achieved SVR12 rates of 80.6% in patients with genotype 3 CHC[18]. Although they compared six treatment regimens, when we compare the above mentioned regimens, they had reduced virological response as compared to results of this study. This may be due to small number of patients treated with these regimens, more percentage of treatment experienced patients and many patients who were co-infected with other infections like HIV.

Various studies have been conducted in Pakistan on efficacy of sofosbuvir based regimens. They have shown different results in different settings. One study demonstrated the efficacy of sofosbuvir and ribavirin given for 24 weeks in patients with genotype 3 and found out rapid virological response at 4 weeks to be 91%, ETR 96.5% and SVR12 to be 85.5%[19]. When we compare their results they contradict the results of this study. These different results may be due to bigger sample size as compared to group B of this study and more treatment experienced patients were present as compared to this study leading to different results.

In another study conducted in Pakistan comparing both regimens found out that ETR in patients treated with sofosbuvir and ribavirin compared to sofosbuvir, peginterferon and ribavirin was 94.86% and 92.42% while SVR12 was 81.71% and 84.85% in both groups respectively[20]. Their results are different from result of this study. These may be due to different sample sizes in their study. However they concluded that both therapies are effective which support the results of this study.

Another study compared the efficacy of 24 weeks sofosbuvir and ribavirin to 12 weeks sofosbuvir, peg-interferon-α-2a and ribavirin in Pakistani population. They demonstrated 100% ETR and 99.17% SVR after 12 weeks of therapy with daily sofosbuvir and ribavirin. Patients who were treated with 12 weeks sofosbuvir, peg-interferon and ribavirin, ETR was 99.62% while SVR12 was 97.91%[21]. Their study showed better results compared to this study. This may be due to the fact that their results were not available for all patients included in their study thus this contradiction can be ignored.

Another Pakistani study done using peglated interferon, sofosbuvir and ribavirin in patients with genotype 3 and results showed 100% SVR12 rates in treatment naive patients, 92% in patients who were non-responders to conventional interferon plus ribavirin and 88% in patients non-responders to peglated interferon and ribavirin[22]. When compared to results of group A of this study, it shows similar results. Thus further validating our results.

When comparing the superiority of either regimen in treatment of chronic hepatitis C, Satsangi et al. concluded that dual therapy with sofosbuvir and ribavirin was equally effective as triple therapy with interferon, sofosbuvir and ribavirin[8]. Similarly Ahmed et al.[9] and Sidhu et al.[11] also had same findings when comparing both of these treatment regimens. This study also did not showed any statistically significant superiority of either of sofosbuvir and ribavirin alone or peg-interferon, sofosbuvir and ribavirin in treatment of CHC genotype 3. Thus validating our results.

This is probably one of few studies comparing sofosbuvir plus ribavirin with or without interferon in a Pakistani population conducted in hepatitis C genotype 3 patients. The limitations of study are neither baseline laboratory investigations nor side effect profiles of patients were noted. A small number of patients lost follow-up after achieving the ETR which also may change the results. Small comparative sample size was available because interferon based therapy was a valid option until the availability of new directly acting antivirals and regimen was discontinued due to change in guidelines. Further comparative studies should be carried out to study the efficacy of sofosbuvir based regimens in Pakistani population and a possible role of peg-interferon-α should be evaluated especially in patients who result in treatment failure after the use of DAAs as limited number of DAAs is available in Pakistan.

CONCLUSION

Dual and triple therapy regimens are equally effective in treating patients having chronic hepatitis C genotype 3.

AUTHOR'S CONTRIBUTION

Butt Z: Conceived idea, Data collection, Manuscript final reading and approval

Shah SMA: Designed research methodology, Literature search, Literature review, Data interpretation, Statistical analysis, Manuscript writing

Talat SU: Data collection and compilation, Literature review

Ajmal M: Manuscript final reading, critical review and approval

Younis I: Data collection, Literature search
Afzal M: Manuscript final reading, Critical review and approval

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