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ORIGINAL ARTICLE

Prospective Study

Dramatic response of hepatitis C patients chronically infected with hepatitis C virus genotype 3 to sofosbuvir-based therapies in Punjab, Pakistan: A prospective study

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Abstract

AIM

To prospectively evaluate the efficacy of sofobuvir (SOF) in hepatitis C patients infected with hepatitis C virus (HCV) genotype 3 in Pakistan.

METHODS

The present study was performed with the coordination of gastroenterology and pathology departments of Shalamar Hospital Lahore from August 2014 to May 2016. The total number of patients included in this study was 1375 and all of them were infected with HCV genotype 3. On the basis of drug combinations, all the patients were separated into two groups. The first group of patients was treated for 24 wk with SOF (Sovaldi® by Gilead Sciences) plus ribavirin (RBV) [Ribazol® by Getz Pharma Pakistan (PVT) Ltd], while the patients of the second group were treated with SOF + RBV + pegylated-interferon (pegIFN) alfa-2a (Ropegra by Roach) for 12 wk. HCV genotyping and viral load measurement were performed on fully automated Abbott Real-Time PCR system (Abbott m24sp automated nucleic acid extraction system and Abbott m2000rt amplification system; abbott Molecular, Des Plaines, IL, United States). For the assessment of sustained virological response (SVR), all HCV RNA negative patients were followed for 12

weeks after the treatment completion. Any patient with less than 12 IU/mL viral load after 12 wk of treatment completion was considered as a sustained virological responder (SVR-12).

RESULTS

A total of 1375 patients chronically infected with HCV genotype 3 were treated with two drug combinations SOF + RBV and SOF + RBV + pegIFN alfa-2a. On the basis of these drug combinations, patients were divided into two groups (first and second). Overall SVR-12 was excellent in both groups (99.17% and 97.91%). Older patients (> 40 years) of second group showed lower SVR-12 (93.46%) compared to first group older patients (98.79%), while in the younger patients of both groups, the SVR-12 rate was almost the same (99.54% in first group and 99.05% in second group). No such difference regarding SVR-12 rate was seen in males and females of first group patients (99.68% and 98.88%, respectively), while in second group the males were found to be better responders compared to females (98.96% and 95%). The SVR-12 rate in previously treated patients of first group was better (99.34%) than second group (93.70%), while naïve patients of second group were marginally better responders (99.25%) than first group (97.80%). Rapid viral response at week-4 was found to be a very effective predictor for assessing the SVR rate at this stage of therapy in both groups. Headache, anemia and fatigue were common side effects in both groups either treated with SOF + RBV or SOF + RBV + pegIFN alfa-2a, while the overall percentage of the side effects was higher in second group.

CONCLUSION

The remarkable SVR response rate of HCV genotype 3 infected patients to SOF provided a new way to look forward to eliminate hepatitis C from our region.

Key words: Sofosbuvir; Sustained virological response; Pakistan

Core tip: Previously, hepatitis C was treated with interferon-based therapies. Intolerable side effects, prolonged treatment duration and unsatisfactory response rates were the major droughts of those therapies. The introduction of sofobuvir (SOF) was claimed as a highly responding oral drug for hepatitis C patients, with minimal side effects in different trials; thus, it was important to assess its efficacy in our population. We found an outstanding response rate of SOF in hepatitis C patients infected with genotype 3 of hepatitis C virus. These findings revealed that with SOF we may eliminate hepatitis C from our population.

Iqbal S, Yousuf MH, Yousaf MI. Dramatic response of hepatitis C patients chronically infected with hepatitis C virus genotype 3 to sofosbuvir-based therapies in Punjab, Pakistan: A prospective study. *World J Gastroenterol* 2017; 23(44): 7899-7905 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i44/7899.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i44.7899

INTRODUCTION

Approximately 2%-3% of the world's population (about 170 million) is chronically infected with hepatitis C virus (HCV)[1]. Prevalence of hepatitis C only in Europe and United States was estimated as 0.2%-2%[2,3]. In Pakistan, the situation regarding HCV infection rate was alarming. About 5.5% Pakistani population was infected with HCV; out of those 60%-80% had HCV genotype 3[4-6]. Hepatitis C patients always remain at risk for developing higher stages of disease like decompensated liver cirrhosis or hepatocellular carcinoma (HCC) that need liver transplantation[7-9].

Since the late 1980s, different categories of conventional interferon were known as a "key drug" to treat hepatitis C patient[10]. Although, the addition of RBV and improvement of conventional interferon with pegylation had enhanced the rate of sustained virological response (SVR)[11-13], yet most of the cases remained non-responders or relapsed after the termination of the treatment.

Because of prolonged treatment, adverse side effects and low SVR rates of interferon plus RBV based therapies, there was a need to improve the long-term viral clearance rate with more effective and less side effects containing drug for hepatitis C patients. In recent trials, newly approved drug "Sofosbuvir" drastically improved the SVR rate[14-16]. Sofosbuvir is thought the next milestone in the advancement of medication for hepatitis C[15]. Sofosbuvir is a nucleotide analogue that acts directly on virus and inhibits polymerase coding region NS5B of HCV and is thought to be more effective direct acting antiviral drug. Sofobuvir is also thought that it has rare side effects as compared to different categories of interferon those were associated with a long list of side effects[17-19].

Although some studies from Pakistan especially from province Punjab were reported regarding SOF based therapies response in HCV genotype 3 infected patients[20,21], yet the efficacy of SOF on such a large scale was never evaluated previously in this region. The main objective of the present study was to assess the response and side effects of SOF in hepatitis C patients infected with genotype 3. Additionally, we were also interested to see the influence of patient's age, gender and baseline viral load on treatment response and to evaluate the association of rapid viral response (RVR) at week-4 with SVR that may help to predict the viral response rate at the earliest stage of the treatment.

MATERIALS AND METHODS

Patients and study design

From August 2014 to May 2016, 1375 patients having chronic infection of HCV genotype 3 were registered at the Department of Gastroenterology in Shalamar Hospital Lahore. Out of these 1375 patients, 885

(64.36%) were either non-responders or relapsers against pegIFN alfa-2a plus RBV and 490 (35.64%) were naive. According to the drug combinations, all the patients were separated into two groups. Patients of the first group were treated with SOF (Sovaldi® by Gilead Sciences) and RBV (Ribazol® by Getz Pharma Pakistan (PVT) Ltd). For the patients of the second group; pegIFN alfa-2a (Ropegra by Roach) was added with SOF + RBV.

Before starting the treatment; baseline characteristics, clinical data and laboratory investigations of all the patients was collected. All the patients included in the present study adults with more than 18 years of age were infected with HCV genotype 3. Out of 1375 patients, 696 (50.62%) were males and 679 (49.38%) were females. HCV genotyping and viral load measurement was performed on fully automated Abbott Real-Time PCR system (Abbott m24sp automated nucleic acid extraction system and Abbott m2000rt amplification system, Abbott Molecular, Des Plaines, IL, United States). Viral load was measured at day-0, week-4 and week-12 of the treatment in the first group and at day-0, week-4 and week-24 in the second group. To evaluate the SVR rate, PCR for HCV RNA was done at week-12 after the termination of treatment. Limit of detection or limit of quantitation was 12 IU/mL on Abbott Real-Time PCR system.

Approved recommendations were followed to treat the patients[22]. The first group was treated for 24 wk with SOF + RBV. For the second group, pegIFN alfa-2a was included with SOF and RBV and treatment duration was reduced to 12 wk. SOF of 400 mg was given as a single pill per day and the dosage of RBV was adjusted according to the patient's body weight (1000-1200 mg/d). For the second group, additional 180 μg of pegIFN alfa-2a was subcutaneously injected once in a week.

Statistical analysis

Continuous data like age, hemoglobin was expressed as mean ± SD, whereas categorical data was expressed in the form of frequencies, proportion and percentages. A 95%CI was also calculated for various proportions. A $P < 0.05$ was considered statistically significant. Statistical analysis was performed using Epicalc 2000 software (version 1.2, Brixton Health, United States).

RESULTS

In the present study, 1375 patients, including 50.62% males and 49.38% females with chronic infection of HCV genotype 3 were enrolled. Out of 1375, 35.64% patients were fresh and 64.36% had previous treatment history of pegIFN alfa-2a + RBV (Table 1).

The response of first group patients was 100% (847/847) to SOF + RBV at the end of therapy (ETR). From 847 ETR responders 840 (99.17%) could sustain their response after 12 weeks of the therapy termination and were declared as SVR-12 responders. In the second group, 526 (99.62%) out of 528 patients showed response at the time of treatment completion and 515 (97.91%) out of 526 were able to sustained their response (SVR-12) (Tables 2 and 3).

Table 1 Baseline characteristics of the patients

Characteristics	Value
Total participants (*n*)	1375
mean age (yr) mean ± SD (range)	48 ± 13 (18-65)
Gender	
Male	696 (50.62%)
Female	679 (49.38%)
Treatment history	
Treatment naive	490 (35.64%)
Treatment experienced	885 (64.36%)
Laboratory investigations	
Hemoglobin(Hb) (g/dL), mean ± SD (range)	12.50 ± 3.50 (7.5-18.3)
Platelets (10^3/μL), mean ± SD (range)	160 ± 76 (50-450)
Creatinine (mg/dL)	0.65 ± 0.22 (0.38-1.50)
Mean viral load (10^6 IU/mL) mean ± SD (range)	3.54 ±2.56 (0.01-33.98)
HCV genotype 3	1375 (100%)

HCV: Hepatitis C virus.

The rate of relapse cases was higher (6.54%) in old age patients (> 40 years) of the second group as compared to first group's old age patients (1.21%). In less than 40 years of age from First and second group's patients the rate of relapse cases was on the lower side (0.46% and 0.95%) (Table 2 and 3). In previously treated patients of the First group, SVR-12 was higher (99.34%) than naïve patients (97.80%) while, in second group, the SVR-12 rate of previously treated patients was lower than naïve (93.70% and 99.25% respectively) (Tables 2 and 3).

Males of both groups were found better responders than females in the present study. In the first group the difference in the response (SVR-12) of males and females was marginal (99.68% and 98.88%, respectively) as compared to second group where the SVR-12 of males and females was examined 98.96% and 95% (Tables 2 and 3).

The SVR-12 rate of the patients from both groups was higher (99.68% and 99.05% respectively) who had less than or equal to 2 MIU/mL of HCV viral load at day-0 than the patients having more than 2 MIU/mL viral load at that stage (97.70% and 96.19% respectively) (Tables 4 and 5). The RVR of the patients (week-4 response) was found very effective predictor to assess the SVR rate at earlier stages of the study. All the patients with HCV RNA negative after four weeks of the treatment (week-4) were also able to sustain their response after 12 weeks of the treatment completion either they belong to first or second group. One patient from the first group (0.19%) and four from the second group (1.05%), who were not able to drop more than two logs of the viral load at the fourth week of the treatment but were negative at the end of treatment, relapsed within 12 wk after the treatment termination. The rate of SVR-12 from both groups was found lower (64.70% from first group and 76.67%

Table 2 Association of baseline characteristics of the patients with sustained virological response treated with sofosbuvir + ribavirin (First group) *n* (%)

Baseline characteristics (*n* = 847)	ETR (*n* = 847), overall ETR = 100%	SVR (*n* = 840), overall SVR = 99.17%	Relapse (*n* = 7), overall relapse rate = 0.83%
Age (yr)			
≤ 40 (*n* = 435)	435 (100)	433 (99.54)	2 (0.46)
> 40 (*n* = 412)	412 (100)	407 (98.79)	5 (1.21)
Previous antiviral treatment history			
Naïve (*n* = 91)	91(100)	89 (97.80)	2 (2.20)
Treated (*n* = 756)	756 (100)	751 (99.34)	5 (0.66)
Gender			
Male (*n* = 310)	310 (100)	309 (99.68)	1 (0.32)
Female (*n* = 537)	537 (100)	531 (98.88)	6 (1.12)

ETR: End of therapy response rate; SVR: Sustained virological response.

Table 3 Association of baseline characteristics of the patients with sustained virological response treated with sofosbuvir + ribavirin + peg-interferon alfa-2a (Second group) *n* (%)

Baseline characteristics (*n* = 528)	ETR (*n* = 526), overall ETR 0.9962	SVR (*n* = 515), overall SVR 0.9791	Relapse (*n* = 11), overall relapse rate = 2.09%
Age (yr)			
≤ 40 (*n* = 419)	419 (100)	415 (99.05)	4 (0.95)
> 40 (*n* = 109)	107 (98.17)	100 (93.46)	7 (6.54)
Previous antiviral treatment history			
Naïve (*n* = 399)	399 (100)	396 (99.25)	3 (0.75)
Treated (*n* = 129)	127 (98.45)	119 (93.70)	8 (6.30)
Gender			
Male (*n* = 386)	386 (100)	382 (98.96)	4 (1.04)
Female (*n* = 142)	140 (98.59)	133 (95)	7 (5)

ETR: End of therapy response rate; SVR: sustained virological response.

Table 4 Association of baseline characteristics of the patients with sustained virological response treated with sofosbuvir + ribavirin (First group) *n* (%)

Time point	Viral load (*n* = 847)	ETR (*n* = 847), overall ETR = 100%	SVR (*n* = 840), overall SVR = 99.17%	Relapse (*n* = 7), overall relapse rate = 0.83%
Baseline (d-0)	≤ 2 MIU/mL (*n* = 630)	630 (100)	628 (99.68)	2 (0.32)
	> 2 MIU/mL (*n* = 217)	217 (100)	212 (97.70)	5 (2.30)
RVR (weeks-4)	Negative (*n* = 290)	290 (100)	290 (100)	0 (0)
	≥ 2 log drop (*n* = 540)	540 (100)	539 (99.81)	1 (0.19)
	< 2 log drop (*n* = 17)	17 (100)	11 (64.70)	6 (35.30)

ETR: End of therapy response rate; SVR: Sustained virological response.

from second group) in those patients who were unable to drop more than two logs of viral load at week-4 (Tables 4 and 5).

The most common side effects in the patients of both group were headache, fatigue and anemia. Excluding hashimoto's thyroiditis, rash, acute psychosis, Bell's palsy and intracranial hemorrhage the percentage of other side effects was higher in the patients of second group in which pegIFN alfa-2a was included with SOF+RBV as compared to first group patients treated without pegIFN alfa-2a. Three cases of Bell's palsy from the first group and one from the second group were new findings of the present study. Intracranial hemorrhage (ICH) was also found in two patients of the first group only but not in second group's patients (Table 6).

DISCUSSION

The main purpose of antiviral therapy in hepatitis C is either to eradicate the infection from the patient's body or to slow down the chances of disease progression to advanced stages like cirrhosis and HCC[23]. Before the introduction of SOF, hepatitis C was treated with interferon and RBV. The response rate of those drugs was not satisfactory. The patient also had to face many side effects of those drugs for a long time due to prolonged therapy durations. The addition of SOF in the antiviral

Table 5 Association of baseline characteristics of the patients with sustained virological response treated with sofosbuvir + ribavirin + peg-interferon-alfa-2a (Second group) *n* (%)

Time point	Viral load (n = 528)	ETR (n = 526), overall ETR 0.9962	SVR (n = 515), overall SVR 0.9791	Relapse (n = 11), overall relapse rate = 2.09%
Baseline (d-0)	⩽ 2 MIU/mL (n = 316)	316 (100)	313 (99.05)	3 (0.95)
	> 2 MIU/mL (n = 212)	210 (99.06)	202 (96.19)	8 (3.81)
RVR (weeks-4)	Negative (n = 116)	116 (100)	116 (100)	0 (0)
	⩾ 2 log drop (n = 380)	380 (100)	376 (98.95)	4 (1.05)
	< 2 log drop (n = 32)	30 (93.75)	23 (76.67)	7 (23.33)

ETR: End of therapy response rate; SVR: Sustained virological response; RVR: Rapid virological response.

Table 6 Side effects (n = 1375) *n* (%)

Side effects	SOF + RBV (n = 847)	SOF + RBV + Peg (n = 528)	*P* value
Headache	248 (29.28)	198 (37.50)	0.083
Fatigue	147 (17.36)	168 (31.82)	0.001
Myalgia	38 (4.49)	43 (8.14)	0.830
Hashimoto's thyroiditis	2 (0.23)	1 (0.19)	0.001
Decreased appetite	71 (8.38)	89 (16.86)	0.179
Rash	7 (0.82)	3 (0.57)	0.001
Thrush	23 (2.71)	19 (3.60)	0.467
Hair loss	8 (0.94)	59 (11.17)	0.781
Aggressiveness	29 (3.42)	38 (7.20)	0.895
Pruritus	69 (8.14)	57 (10.79)	0.959
Insomnia	79 (9.32)	63 (11.93)	0.498
Depression	36 (4.25)	67 (12.69)	0.006
Acute psychosis	8 (0.94)	3 (0.57)	0.776
Hematologic abnormalities			
Anemia (< 10 g/dL)	238 (28.10)	215 (40.72)	0.001
Leukocytopenia (< $3 \times 10^3/\mu L$)	16 (1.89)	61 (11.55)	0.001
Thrombocytopenia (< $100 \times 10^3/\mu L$)	64 (7.56)	72 (13.64)	0.188
Bell's Palsy	3 (0.35)	1 (0.19)	0.628
Intracranial hemorrhage	2 (0.23)	0 (0)	

therapy regimen has not only dramatically improved the SVR rate, but has also minimized the side effects[23].

Sofosbuvir is a nucleotide analogue that acts as a NS5B polymerase inhibitor. It has become the key drug to treat the patients of hepatitis C[17-19,24,25]. No virological breakthrough (HCV RNA negative patients at early stages of therapy became again positive during the therapy) was examined so far in the previous studies in which SOF was used as part of drug combinations in hepatitis C patients[24, 26]. The same situation was observed in our findings where no virological breakthrough was seen. It confirms the efficacy of SOF based therapies.

The overall SVR-12 rate in first and second group was 99.17% and 97.91% respectively. These findings show that the addition of SOF in drug combinations for hepatitis C patients infected with genotype 3 is more effective as compared to the treatment regimen without SOF as was reported before[22-24]. This is encouraging to eliminate the hepatitis C disease from the Pakistani population where most of the patients are infected with HCV genotype 3[27-29].

Our findings also advocate that 12 wk regimen containing SOF + RBV + pegIFN alfa-2a is equally effective as the 24 wk regimen of SOF + sRBV in HCV genotype 3 patients. It indicates that the pegIFN is still effective if given with SOF based regimen. With the SOF + RBV + pegIFN alfa-2a combination, treatment duration and cost could also be cut down in HCV genotype 3 cases. But, more side effects due to pegIFN as shown in this study may be the major disadvantage.

The patients less than 40 years of age were better responders in both groups as compared to the patients with more than 40 years of age. The better response of younger group patients treated with pegIFN+RBV was also indicated in our[30] and many other previous studies reported from different areas of the world before the introduction of SOF[29, 30]. It revealed that younger group patients with hepatitis C are suitable candidates to treat. Intolerance of old age patients (More than 40 years) as compared to young patients (Less than 40 years) against pegIFNs may be a major cause of lower SVR-12 rate in older patients as was also indicated previously[30-32]. It shows that the use of SOF without pegIFN alfa-2a is more effective, especially in old age patients and it may help to manage the hepatitis C patient's treatment regimen in the future.

The SVR-12 rate of previously treated patients was higher in first group patients (99.34%) than the second group (93.46%). It indicates that six months therapy of SOF + RBV is more effective in previously non-

responders or relapsed patients to pegIFN alfa-2a + RBV and infected with HCV genotype 3 as compared to three months therapy of SOF + RBV + pegIFN alfa-2a. On the other hand, SVR-12 rate of naïve patients was on higher side in second group's patients compared to first group's patients. It revealed that in naïve patients, treatment could be reduced from six to three months with the addition of pegIFN alfa-2a.

Interestingly, the RVR rate at week-4 was found a good predictor of SVR in both groups. All HCV RNA negative patients at week-4 were also found SVR-12 responders either they belongs to first or second group. The SVR rate of both group patients who were able to drop more than two log viral load at week-4 of the therapy was more satisfactory as compared to those who were unable to drop more than two log viral load at that stage. The effect of baseline (Day-0) viral load was not so significant in the present study.

The overall percentage of side effects was higher in the patients treated with triple therapy regimen (SOF + RBV + pegIFN alfa-2a) as compared to those patients treated with double therapy regimen (SOF + RBV). Headache, fatigue and anemia were the common side effects in all the patients either treated with or without pegIFN alfa-2a. Myalgia, decreased appetite, hair loss, aggression, depression, leukocytopenia and thrombocytopenia were prominently on the higher side in the patients of the second group as compared to first group's patients. It was also reported previously in RBV and pegIFN alfa-2a treated patients[33].

Severe neuropsychiatric side effects were commonly reported previously in hepatitis C patients treated with pegIFN and RBV[33, 34]. Sometimes treatment has to discontinue because of the severity of such adverse side effects. But in newly introduced antiviral drug "SOF" the severe neuropsychiatric complications are not much reported so far.

Two cases of intracranial hemorrhage were found only in first group's patients. Intracranial hemorrhage was also reported before in untreated hepatitis C patients[35,36], but no evidence of ICH with pegIFN plus RBV was seen previously. In our findings ICH may also be due to HCV not because of SOF that needs further studies on a large scale.

In conclusion, SOF (SOVALDI®) based therapy was found safe, effective and well tolerated by the patients infected with HCV genotype 3 in Pakistan. Higher SVR rate of the present study indicates that this is the right time for full blooded attack on HCV to get rid of it permanently from our region. To achieve the target, there is a need of policy under the aegis of the Federal Government to provide drugs on discounted rates or free for non-affording patients.

COMMENTS

Background

In Pakistan about 5.5% population is infected with hepatitis C virus (HCV), out of those 60%-80% has HCV genotype 3. Due to lower response and intolerable side effects of peg-Interferon plus RBV therapy, it was difficult to treat hepatitis C patients in past. In recent trials, the newly introduced oral drug "Sofosbuvir" was claimed for its remarkable response in the chronically infected patients with HCV genotype 2 and 3. It was important to see its efficacy in Pakistani population where most of the patients were infected with HCV genotype 3.

Research frontiers

Outcomes of the present study revealed that the SOF is more effective drug to treat the hepatitis C patients especially infected with genotype 3 of HCV. Sofosbuvir has less side effects and short treatment duration that helps the patient to get relief from hepatitis C in short time. These outcomes are also encouraged to eliminate hepatitis C from Pakistan where most of the population is infected with genotype 3 of HCV.

Innovations and breakthroughs

The novel finding of this study was to find highly responding oral drug (SOF) with low side effects that may help to eradicate hepatitis C from Pakistan where most of the population is infected with HCV genotype 3. Furthermore, we were also able to declare that the use of SOF is equally effective with or without peg-Interferon that may also help to avoid the adverse side effects of peg-Interferon injections. Its better response in all age groups also make easy to the clinician to treat the hepatitis C patients of all age groups.

Applications

The use of this oral drug (SOF) that has a dramatic response rate in hepatitis C patients will help to eliminate hepatitis C from Pakistan. To achieve the target, there is a need for policy under the aegis of the Federal Government to provide free drugs or on discounted rates for non-affording.

Terminology

Scientific terms that have been used in this manuscript are familiar with most readers and have been described comprehensively in different sections of the manuscript.

Peer-review

The authors carried out a prospective study to assess the efficacy and safety of SOF based therapies for the patients with HCV genotype 3. This study is well designed and the results are relevant to clinical practice.

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