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***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**

Iqbal S *et al*. Response of sofosbuvir in HCV patients

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**Abstract**

# *AIM*

To prospectively evaluate the efficacy of Sofosbuvir (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. A 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. First group patients were 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 + peg-IFN alfa-2a (Ropegra by Roach) for 12 wk. 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). To assess sustained virological response (SVR), all HCV RNA negative patients were followed for 12 wk after the treatment completion. The patient with less than 12 IU/mL viral load after 12 wk of treatment completion was considered as 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 1st and 2nd. Overall sustained virological response after 12 wk of therapy termination (SVR-12) was excellent in both groups (99.17% and 97.91%). Older patients (> 40 years) of 2nd group showed lower SVR-12 (93.46%) as compared to 1st group patients (98.79%), while in the younger patients of both groups SVR-12 rate was almost same (99.54% in 1st group and 99.05% in 2nd group). No such difference regarding SVR-12 rate was seen in males and females of 1st group patients (99.80% and 98.88%, respectively), while in the 2nd group, males were found better responders as compared to females (98.95% and 95%). The SVR-12 rate in previously treated patients of 1st group was better (99.34%) than 2nd group (93.70%), while naïve patients of 2nd group were marginally better responders (99.25%) than 1st group (97.80%). Rapid viral response (RVR) at week-4 was found very effective predictor to assess 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 the 2nd 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

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**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 Sofosbuvir (SOF) that was claimed highly responding oral drug for hepatitis C patients with its minimal side effects in different trials, it was important to see its efficacy in our population. We found the 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.

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## INTRODUCTION

Approximately, 170 million population worldwide was chronically infected by Hepatitis C virus (HCV) that represents 2%-3% of the world population[1]. Prevalence of Hepatitis Conly in Europe and United States was estimated 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 remained at risk for developing higher stages of disease like decompensated liver cirrhosis or hepatocellular carcinoma (HCC) that needed liver transplantation otherwise risk may elevated to mortality[7-9].

Since the late 1980s, different type of conventional Interferons were known as akey drug to treat Hepatitis C patient[10]. Although, with 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 (SOF)” drastically improved the SVR rate[14-16]. SOF is thought the next milestone in the advancement of medication for Hepatitis C[15]. SOF is a nucleotide analogue that acts directly on virus and inhibits polymerase coding region NS5B of HCV and is thought more effective direct acting antiviral drug with rare side effects as compared to interferons 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[20-22], yet the efficacy of SOF on such a large scale was never evaluated previously in Pakistan. 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. Of 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 1st 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 were infected with HCV genotype 3 with more than 18 years of age. Out of 1375 patients, 696 (50.62%) were males and 679 (49.38%) 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[23]. The first group was treated for 24 wk with SOF + RBV. For the 2nd 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/day). 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 expresses in the form of frequencies, proportion and percentages. A 95%CI (confidence interval) 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.](http://www.brixtonhealth.com/about.html) 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 1st 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 wk 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).

The rate of relapse cases was higher (6.54%) in old age patients (> 40 years) of the second group as compared to 1st group’s old age patients (1.21%). In less than 40 years of age from 1st and 2nd group’s patients the rate of relapse cases was on the lower side (0.46% and 0.95%) (Tables 2 and 3). In previously treated patients of the 1st group, SVR-12 was higher (99.34%) than naïve patients (97.80%) while, in 2nd 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 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 (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 wk after the treatment completion. One patient from the 1st group (0.19%) and four from the 2nd 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 was found lower in those patients who were unable to drop more than two logs of viral load at week-4 (Tables 4 and 5).

The common side effects in both group’s patients were headache, fatigue, anemia leukocytopenia, and thrombocytopenia. The percentage of overall side effects was higher in the patients of 2nd group in which pegIFN alfa-2a was included with SOF + RBV as compared to 1st group patients treated without pegIFN alfa-2a. Hair loss, depression and leukocytopenia were found considerably on the higher side in the second group as compared to the first group. On the other side headache, pruritus, Insomnia, and anemia were examined more common in 1st group patients as compared to the second group. Three cases of Bell’s palsy from the first group and one from the second group were rare findings of the present study. Intracranial hemorrhage (ICH) and thrombotic stroke were also were also found in two and one patient respectively from the first group only, no such findings were observed in second group’s patients (Table 6).

**DISCUSSION**

The main purpose of antiviral therapy in hepatitis C is 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[24]. 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 therapy regimen has not only dramatically improved the SVR rate, but has also minimized the side effects[24].

SOF is a nucleotide analogue that acts as a NS5B polymerase inhibitor. It has become the key drug to treat the patients of hepatitis C[17-19,25-26]. No virological breakthrough (HCV RNA negative patients at early stages became 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[25,27]. 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 1st and 2nd 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[23-25]. This is encouraging to eliminate the hepatitis C disease from the Pakistani population where most of the patients are infected with HCV genotype 3[28-30].

Our findings also advocate that 12 wk regimen containing SOF + RBV + pegIFN alfa-2a is equally effective as the 24 wk regimen of SOF + RBV 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. The better response of younger group patients treated without SOF was also indicated in our previous study[31] and many other studies reported from different areas of the world[30,31]. 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 the major cause of a lower SVR rate in older patients as indicated previously[31-33]. 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 rate of previously treated patients was higher in first group patients (99.34%) than the second group. It indicates that six months use of SOF is more effective in pegIFN alfa-2a + RBV non-responders or relapsed patients infected with HCV genotype 3 as compared to three months therapy. On the other hand, in the naïve patients, the response rate of second group patients was observed on the higher side as compared to first group 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. The SVR rate of those patients from both groups was 100% who had no HCV RNA at the fourth week of the treatment. 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 also satisfactory (99.81% in the first group and 98.95% in the second group) 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, anemia and fatigue were common side effects in all the patients either treated with or without pegIFN-alfa-2a. Hair loss, depression and leukocytopenia were on the high side in the patients of the second group as compared to first group that were also reported previously in RBV and pegIFN alfa-2a treated patients[34]. On the other side headache, pruritus, insomnia, and anemia were examined more common in 1st group patients as compared to the second group (Table 6).

Severe neuropsychiatric side effects were commonly reported in the patients of hepatitis C treated with pegIFN and RBV. Sometimes the severity of such adverse side effects causes discontinuation of the treatment[34-35]. But in newly introduced antiviral drug ‘’SOF’’ the severe neuropsychiatric complications are not much reported so far that was also examined in our findings.

Three cases of Bell’s palsy in the first group and one in the second group were found in the present study. ICH and thrombotic stroke were also found in two and one patient respectively, of the first group only and no such findings were observed in second group patients. It indicates that these side effects were because of SOF or RBV but not due to a pegIFN that was used in the second group (Table 6).

ICH was also reported before in untreated hepatitis C patients [36-37], 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, in the present study, SOF (SOVALDI®) based therapy was found safe, effective and was well tolerated by the patients infected with HCV genotype 3 in Pakistan. Higher SVR rates of the present study indicate that this is the right time for full blooded attack on HCV to get rid of it permanently. To achieve the target, there is a need for policy under the aegis of the Federal Government to provide drugs free or on discounted rates for non-affording.

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**COMMENTS**

***Background***

In Pakistan about 5.5% population is infected with hepatitis C virus (HCV), out of those 60%-80% have HCV genotype 3. Due to lower response and intolerable side effects of peg-Interferon and RBV therapy, it was difficult to treat Hepatitis C patients in past. In recent trials, the newly introduced oral drug “Sofosbuvir (SOF)” 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.

***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. SOF has less side effects and short treatment duration that helps the patients 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 found 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-Interferonthat may also help to avoid the adverse side effects of peg-Interferon injections. Its better response in all age groups also make easy for the clinician to treat the Hepatitis C patients of all age groups with SOF.

***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 genotype 3. This study well designed and the results are relevant to clinical practice.

**REFERENCES**

1 **Global Burden Of Hepatitis C Working Group.** Global burden of disease (GBD) for hepatitis C. *J Clin Pharmacol* 2004; **44**: 20-29 [PMID: 14681338 DOI: 10.1177/0091270003258669]

2 **Lavanchy D**. The global burden of hepatitis C. *Liver Int* 2009; **29** Suppl 1: 74-81 [PMID: 19207969 DOI: 10.1111/j.1478-3231.2008.01934.x]

3 **Esteban JI**, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. *J Hepatol* 2008; **48**: 148-162 [PMID: 18022726 DOI: 10.1016/j.jhep.2007.07.033]

4 **Attaullah S**, Khan S, Ali I. Hepatitis C virus genotypes in Pakistan: a systemic review. *Virol J* 2011; **8**: 433 [PMID: 21902822 DOI: 10.1186/1743-422X-8-433]

5 **Qazi MA,** Fayyaz M, Chaudhary GMD, Jamil A, Malik AH, Gardezi AI, Bukhari MH. Hepatitis C virus genotypes in Bahawalpur. *Biomedica* 2006; **22**: 51-54

6 **Ahmad S,** Salati SAA, Mattar EH, Al-Sabban AMH, Hamad AM. Epidemiology of Hepatitis C Virus (HCV) Infection. *Physicians Academy* 2010; **4**: 82-87

7 **Davis GL**, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl* 2003; **9**: 331-338 [PMID: 12682882 DOI: 10.1053/jlts.2003.50073]

8 **Verna EC**, Brown RS Jr. Hepatitis C virus and liver transplantation. *Clin Liver Dis* 2006; **10**: 919-940 [PMID: 17164125 DOI: 10.1016/j.cld.2006.08.012]

9 **El-Serag HB**, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999; **340**: 745-750 [PMID: 10072408 DOI: 10.1056/NEJM199903113401001]

10 **Davis GL**, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC Jr, Perrillo RP, Carey W, Jacobson IM, Payne J, Dienstag JL; Hepatitis Interventional Therapy Group. Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter randomized, controlled trial. *N Engl J Med* 1989; **321**: 1501-1506 [PMID: 2509916 DOI: 10.1056/NEJM198911303212203]

11 **McHutchison JG**, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, Goodman ZD, Ling MH, Cort S, Albrecht JK. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med* 1998; **339**: 1485-1492 [PMID: 9819446 DOI: 10.1056/NEJM199811193392101]

12 **Manns MP**, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958-965 [PMID: 11583749 DOI: 10.1016/S0140-6736(01)06102-5]

13 **Fried MW**, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975-982 [PMID: 12324553 DOI: 10.1056/NEJMoa020047]

14 **Liu X**, Wang Y, Zhang G, Li N, Zhu Q, Chang H, Han Q, Lv Y, Liu Z. Efficacy and safety of sofosbuvir-based therapy for the treatment of chronic hepatitis C in treatment-naïve and treatment-experienced patients. *Int J Antimicrob Agents* 2014; **44**: 145-151 [PMID: 25034873 DOI: 10.1016/j.ijantimicag.2014.04.018]

15 **Steinebrunner N**, Sprinzl MF, Zimmermann T, Wörns MA, Zimmerer T, Galle PR, Stremmel W, Eisenbach C, Stein K, Antoni C, Schattenberg JM, Pathil A. Early virological response may predict treatment response in sofosbuvir-based combination therapy of chronic hepatitis c in a multi-center "real-life" cohort. *BMC Gastroenterol* 2015; **15**: 97 [PMID: 26239732 DOI: 10.1186/s12876-015-0328-9]

16 **Korean Association for the Study of the Liver.** KASL clinical practice guidelines: management of hepatitis C. *Clin Mol Hepatol* 2016; **22**: 76-139 [PMID: 27044763 DOI: 10.3350/cmh.2016.22.1.76]

17 **Murakami E,** Tolstykh T, Bao H, Niu C, Steuer HM, Bao D, Chang W, Espiritu C, Bansal S, Lam AM, Otto MJ, Sofia MJ, Furman PA. Mechanism of activation of PSI-7851 and its diastereoisomer PSI-7977. *J BioChem* 2010; **285**: 34337-34347 [PMID: 20801890 DOI: 10.1074/jbc.M110.161802]

18 **Lam AM**, Murakami E, Espiritu C, Steuer HM, Niu C, Keilman M, Bao H, Zennou V, Bourne N, Julander JG, Morrey JD, Smee DF, Frick DN, Heck JA, Wang P, Nagarathnam D, Ross BS, Sofia MJ, Otto MJ, Furman PA. PSI-7851, a pronucleotide of beta-D-2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate, is a potent and pan-genotype inhibitor of hepatitis C virus replication. *Antimicrob Agents Chemother* 2010; **54**: 3187-3196 [PMID: 20516278 DOI: 10.1128/AAC.00399-10]

19 **Gane EJ**, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013; **368**: 34-44 [PMID: 23281974 DOI: 10.1056/NEJMoa1208953]

20 **Akhter TS**, Umar M, Khaar HT, Aslam F, Nisar G, Naseer A, Ahmad S, Osama M. Sofosbuvir For The Treatment Of Hepatitis C Genotype 3 Infected Patients In Pakistan. *J Ayub Med Coll Abbottabad* 2016; **28** (Suppl 1): S884-S889 [PMID: 28782338]

21 **Wahid B**, Saleem K, Ali A, Rafique S, Idrees M. Rising relapse rate in hepatitis C virus type 3a-infected patients against sofosbuvir and ribavirin combination therapy: a Pakistani experience. *Eur J Gastroenterol Hepatol* 2017; **29**: 979-980 [PMID: 28471832 DOI: 10.1097/MEG.0000000000000895]

22 **Lawitz E**, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, DeJesus E, Pearlman B, Rabinovitz M, Gitlin N, Lim JK, Pockros PJ, Scott JD, Fevery B, Lambrecht T, Ouwerkerk-Mahadevan S, Callewaert K, Symonds WT, Picchio G, Lindsay KL, Beumont M, Jacobson IM. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet* 2014; **384**: 1756-1765 [PMID: 25078309 DOI: 10.1016/S0140-6736(14)61036-9]

23 **European Association for the Study of the Liver.** EASL recommendations on treatment of hepatitis C 2014. *J Hepatol* 2014; **61**: 373-395 [PMID: 24818984 DOI: 10.1016/j.jhep.2014.05.001]

24 **European Association for Study of Liver.** EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2014; **60**: 392-420 [PMID: 24331294 DOI: 10.1016/j.jhep.2013.11.003]

25 **Lawitz E**, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368**: 1878-1887 [PMID: 23607594 DOI: 10.1056/NEJMoa1214853]

26 **Lange CM**, Zeuzem S. Perspectives and challenges of interferon-free therapy for chronic hepatitis C. *J Hepatol* 2013; **58**: 583-592 [PMID: 23104162 DOI: 10.1016/j.jhep.2012.10.019]

27 **Lawitz E**, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **369**: 678-679 [PMID: 23944316 DOI: 10.1056/NEJMc1307641]

28 **Khan N**, Akmal M, Hayat M, Umar M, Ullah A, Ahmed I, Rahim K, Ali S, Bahadar S, Saleha S. Geographic distribution of hepatitis C virus genotypes in pakistan. *Hepat Mon* 2014; **14**: e20299 [PMID: 25477975 DOI: 10.5812/hepatmon.20299]

29 **Iqbal S,** Ahmad R, Yousaf MH, Mumtaz A, Amin D, Rasool G, Manzoor A. Assessment of major genotypes and subtypes of Hepatitis C virus. *Prof Med J* 2007; **14**: 266-271 Available from: URL: <http://www.pakmedinet.com>

30 **Idrees M**, Riazuddin S. Frequency distribution of hepatitis C virus genotypes in different geographical regions of Pakistan and their possible routes of transmission. *BMC Infect Dis* 2008; **8**: 69 [PMID: 18498666 DOI: 10.1186/1471-2334-8-69]

31 **Iqbal S**, Khalil-Ur-Rahman, Sheikh MA, Arshad M. Response of different HCV genotypes to interferon therapy in different age groups of chronic hepatitis-C patients. *J Ayub Med Coll Abbottabad* 2014; **26**: 310-315 [PMID: 25671935]

32 **Ismail MH**. Prediction of sustained virologic responses to combination therapy of pegylated interferon-α and ribavirin in patients with chronic hepatitis C infection. *J Family Community Med* 2013; **20**: 35-40 [PMID: 23723729 DOI: 10.1086/644507]

33 **Kau A**, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. *J Hepatol* 2008; **49**: 634-651 [PMID: 18715665 DOI: 10.1016/j.jhep.2008.07.013]

34 **Modabbernia A**, Poustchi H, Malekzadeh R. Neuropsychiatric and psychosocial issues of patients with hepatitis C infection: a selective literature review. *Hepat Mon* 2013; **13**: e8340 [PMID: 23550100 DOI: 10.5812/hepatmon.8340]

35 **Guadagnino V**, Trotta MP, Carioti J, Caroleo B, Antinori A; Nocchiero Study Group. Does depression symptomatology affect medication compliance during the first weeks of anti-HCV therapy in intravenous drug users? *Dig Liver Dis* 2006; **38**: 119-124 [PMID: 16297672 DOI: 10.1016/j.dld.2005.10.008]

36 **Tseng CH**, Muo CH, Hsu CY, Kao CH. Increased Risk of Intracerebral Hemorrhage Among Patients With Hepatitis C Virus Infection. *Medicine* (Baltimore) 2015; **94**: e2132 [PMID: 26579831 DOI: 10.1097/MD.0000000000002132]

37 **Karibe H**, Niizuma H, Ohyama H, Shirane R, Yoshimoto T. Hepatitis C virus (HCV) infection as a risk factor for spontaneous intracerebral hemorrhage: hospital based case-control study. *J Clin Neurosci* 2001; **8**: 423-425 [PMID: 11535009 DOI: 10.1054/jocn.2001.0811].]

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**Table 1 Baseline characteristics of the patients *n* (%)**

|  |  |
| --- | --- |
| 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 (103/µL), mean ± SD (Range) | 160 ± 76 (50-450) |
| Creatinine (mg/dL) | 0.65 ± 0.22 (0.38-1.50) |
| Mean viral load (106 IU/mL) mean ± SD (Range) | 3.54 ± 2.56 (0.01-33.98) |
| HCV genotype 3 | 1375 (100.0) |

**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 = 99.62%** | | **SVR (*n* = 515)**  **overall SVR = 97.91%** | | **Relapse (*n* = 11)**  **overall relapse rate = 2.09%** |
| Age (yr) | | | | | | |
| ≤ 40 (*n* = 419) | | 419 (100.0) | | 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 (100.0) | | 396 (99.25) | | 3 (0.75) |
| Treated (*n* = 129) | | 127 (98.45) | | 119 (93.70) | | 8 (6.30) |
| Gender |  | |  | |  | |
| Male (*n* = 386) | | 386 (100.0) | | 382 (98.96) | | 4 (1.04) |
| Female (*n* = 142) | | 140 (98.59) | | 133 (95.00) | | 7 (5.00) |

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** | **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)  > 2 MIU/mL (*n* = 217) | 630 (100.0)  217 (100.0) | 628 (99.68)  212 (97.70) | 2 (0.32)  5 (2.30) |
| RVR (wk-4) | Negative (*n* = 290)  ≥ 2 log drop (*n* = 540)  < 2 log drop (*n* = 17) | 290 (100.0)  540 (100.0)  17 (100.0) | 290 (100.0)  539 (99.81)  11 (64.70) | 0 (0)  1 (0.19)  6 (35.30) |

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

**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** | **ETR (*n* = 526)**  **overall**  **ETR = 99.62%** | **SVR (*n* = 515)**  **overall**  **SVR = 97.91%** | **Relapse (*n* = 11)**  **overall relapse**  **rate = 2.09%** |
| Baseline(d-0) | ≤ 2 MIU/mL (*n* = 316)  > 2 MIU/mL (*n* = 212) | | 316 (100.0)  210 (99.06) | 313 (99.05)  202 (96.19) | 3 (0.95)  8 (3.81) |
| RVR(wk-4) | Negative (*n* = 116)  ≥ 2 log drop (*n* = 380)  < 2 log drop (*n* = 32) | | 116 (100.0)  380 (100.0)  30 (93.75) | 116 (100.0)  376 (98.95)  23 (76.67) | 0 (0)  4 (1.05)  7 (23.33) |

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

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

|  |  |  |  |
| --- | --- | --- | --- |
| **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 (10.792) | 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 × 103/μL) | 16 (1.89) | 61 (11.55) | 0.001 |
| Thrombocytopenia (< 100 × 103/μL) | 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 |  |

SOF + RBV: Sofosbuvir plus ribavirin.