ORIGINAL ARTICLE

Outcome of Patients Treated with Oral Sofosbuvir and Ribavirin: One Year Follow up Experience

Nadeem Islam Sheikh[1], Sajid Naseem[2], Atif Sitwat[3], Ali Yasir[4]

Author`s Affiliation

[1]Assistant Professor, Medicine HBS Medical College, Islamabad
[1]Senior Registrar, Medicine HBS Medical College, Islamabad
[3]Professor, Medicine HBS Medical College, Islamabad
[4]Manager, Clinical Research & Pharmacovigilance, The Searle Company Limited, Karachi

Author`s Contribution

[1]Conceived Idea, ManuScript Writing, [1,2]Data Collection and Literature Review, [1,3,4]Final Reading and Approval, [1,4]Data Interpretation. Statiscal Analysis.

Article Info

Received: Nov 24,2017
Accepted: Mar 15,2018

Funding Source: Nil
Conflict of Interest: Nil

Address of Correspondence
Dr. Nadeem Islam Sheikh
Email: *nadeem.islam@hotmail.com*

ABSTRACT

Objective: The aim of this study was to evaluate the efficacy and safety of sofosbuvir plus ribavirin therapy and prevalence of hepatitis C relapses.

Methodology: A descriptive case series study was planned and executed for the evaluation efficacy, safety and relapsers of among HCV patients treated with sofosbuvir plus ribavirin. One hundred patients were enrolled after careful monitoring of inclusion criteria. PCR, LFTs, CP, RFTs, Serum albumin and ultrasound performed in all patients and they were given 400mg of sofosbuvir and 1000mg of Ribavarin. There was no dropout of haemoglobin and ALT was normalized in both groups

Results: 69% male and 31% females between January 2014 to March 2017. All patients were naive having genotype 3 and the average age in males being 33.3 years whilst in females being 51.61 years. At one-month post treatment, 87.09% females and 78.265% males achieved RVR while ETR was 83.87% in females and 86.95% in males. Treatment-related adverse effects were myalgias, insomnia, and flu like symptoms which need symptomatic treatment. After 3 months of follow up, SVR was observed to be 90.32% in females and 88.405% in males. However, subsequent follow up of 1 patients revealed a relapse rate of 12.9% in females and 8.69% in males after achieving SVR.

Conclusion: The combination of sofosbuvir and ribavarin is safe and effective treatment for genotype 3 (GT3) non cirrhotic patients

Key Word: Sofosbuvir, hepatitis C, ribavirin.

Introduction

The global prevalence of anti-HCV is 1.6% with a Viraemic prevalence of about 1.1%. Roughly 80 million people are affected globally.[1] Genotype I has highest global distribution (46%) followed by genotype 3 (22%).[1] Pakistan has the most astounding number of persons infected with active hepatitis C other than China. [2]

Most prevalent genotype in Pakistan is genotype 3 (GT3) which is present in 79% of cases.[2] Direct acting anti-viral agents (DAA) are now the standard care in patients infected with Chronic Hepatitis C.[3] About 85% of patients remain HCV positive once they acquire the disease.[4]

After 1986 the treatment available for Hepatitis was injection interferon with Ribavirin. Till recent past, the standard treatment of Hepatitis C was a combination of pegylated interferon with Ribavarin.[5] DAA analogue (Sofosbuvir), a nucleotide analogue inhibitor of HCV NS5B polymerase is approved by FDA since 2013 in combination with pegylated interferon and ribavirin for 12 weeks for Genotype I and 4. For Genotype 2, Sofosbuvir and Ribavirin in recommended for 12 weeks and for Genotype 3 (24 weeks).[6]

Genotype 3 patients have higher risk of all worse outcomes as compared to genotype I and 2.[7]

In VALANCE phase III study, the response of sofosbuvir and ribavirin in Genotype 3 patients treated for 24 weeks was 94% (86/92), in cirrhotic naive patients, the response of treatment was 87% and in cirrhotic experienced patients response to treatment was 60%.[8] In Boson study, the addition of pegylated interferon with ribavirin and sofosbuvir showed that treatment duration maybe reduced to 12 weeks for other genotypes.[9]

Due to high prevalence of the hepatitis C in the developing countries, it is needed, not only to treat the patients but also monitor them for reversal. Hence this is study is planned on the

good considered drug for HCV treatment. Results of this study could be a valuable addition in the medical literature for hepatitis C.

Methodology

It was a prospective observational study to see efficacy of oral sofosbuvir and ribavarin in naive patients treated for 24 weeks. The participants of this study were diverse population presented to Social Security Hospital Islamabad between January 2014 to March 2017. Inclusion criteria for starting treatment were age greater than 18 years, reactive anti-HCV antibody and measurable serum HCV RNA by PCR, patients with the compensated liver disease with normal hemoglobin and total leucocyte and platelet count. HCV genotyping was performed in every patient along with LFTs, serum albumin and prothrombin time. Screening of HIV and HBS antigen was performed in every patient. detailed history regarding addiction, occupation and probable mode of transmission entered in every patient on a proforma designed for study after a written consent from patients.

Decompensated chronic liver disease as per ultrasonography, pregnant and breastfeeding women, alcohol abuse and previously treated genotype 3 relapsers or non-responder were excluded from the study. All those patients who fulfilled the inclusion criteria but refused to participate were also not considered for this study.

Sofosbuvir 400mg along with ribavirin 500mg twice daily for patients less than 75kg and 600mg twice daily for patients more than 75kg was used. The primary endpoint was negative HCV RNA at 12 weeks after completion of treatment (SVR 12). The secondary end point was rapid virological response at 4 weeks of treatment (RVR) and end of treatment at 24 weeks (ETR). All enrolled patients were followed for next one year to see the relapse rate.

Treatment-related adverse effects and monthly follow up of patients was done and biochemical profile comprising blood complete picture, liver function test, thyroid function test and renal function test were performed in every patient. Collected data was entered and analyzed using SPSS20 inc. Regression analysis was performed to check the impact of confounding factors. P-value$<$0.05 was considered significant.

Results

A total of one hundred patients with Genotype 3 amongst which 69(69%) were males and 31 (31%) were females. The mean male patient was 33.3 years with a minimum age of 18 and maximum of 75 years. On the other hand, the mean age of female patient was 47 years with a minimum age of 18 and maximum of 55 years. Average haemoglobin of males was 14.2 with total leucocyte count of 4.4 and platelet of $110x10^3$ while average haemoglobin in females was 11.4 with TLC was 5.5 and platelet count of $125x10^3$. The average viral load in males was 338656.5 copies/ml while in females the average viral load was 526125 copies/ml. (Table I)

Table I:Lab parameters of male and female patients

Lab parameters	Males	Females
Haemoglobin(g/dl)	14.2	11.4
Total leucocyte count (10^3)	4.4	6
Platelet count (10^3)	110	125
Serum albumin (grams)	4.4	4.2
ALT	96	126
AST	78	90
PT (seconds)	13	14

The probable mode of transmission in males and females was intravenous or intramuscular injections which carried a risk of about 64.5%.

8.69% males relapsed while 12.9% females relapsed after attaining SVR over one year.(Table I & II)

At one month RVR was positive in 87.09% (27/31) of females while 78.26% (54/69) of male patients. End treatment response (ETR) was positive in 86.95% of males (60/69) while 83.87 % (26/31) females achieved ETR. ALT levels in males reduced to 43 from 96 while in females it decreased from 126 to 60. There was no significant decrease in haemglobin and platelets in both the groups.

After three months of completion of treatment, SVR (sustained virological response) was achieved in 87.09% (27/31) females

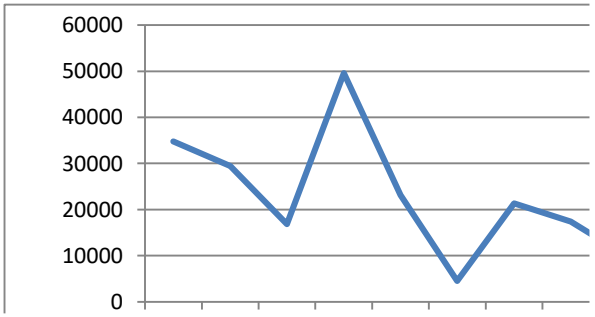
Table II: Viral load and treatment outcome of male patients

Age	18-25	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70	70-75
Number of patient	6	4	8	7	22	3	7	5	4	2	1
Viral load	34768	29476	16874	49574	23142	4517	21342	17431	9832	7360	19357
RVR	6	4	7	5	18	2	5	2	2	2	1
ETR	5	4	6	6	20	3	6	4	4	1	1
SVR	6	4	6	6	20	3	6	4	3	2	1
Relapse	-	-	1	3	-	-	-	2	-	-	-

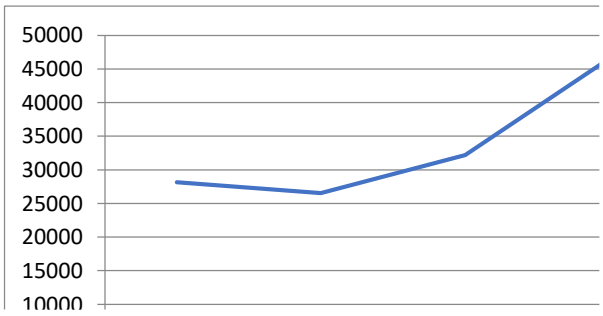
and 88.45% (61/69) males.

In the next one year of follow up of patients 8.69% of the males and 12.9% of female patients relapsed with positive PCR and increase in ALT levels in spite of achieving SVR

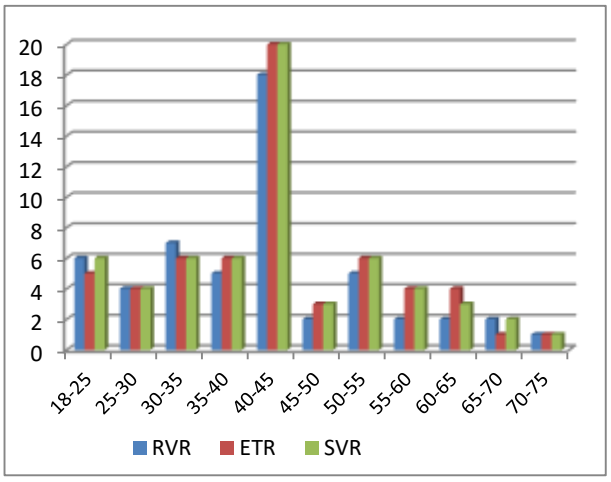
- RVR achieved: 76.26% (54/69)
- ETR achieved: 86.96% (60/69)
- SVR achieved :88.45% (61/69)
- Relapsed after SVR: 8.69%(6/69)
- Treatment failure: 20.24%



Graph#1: Viral load in males



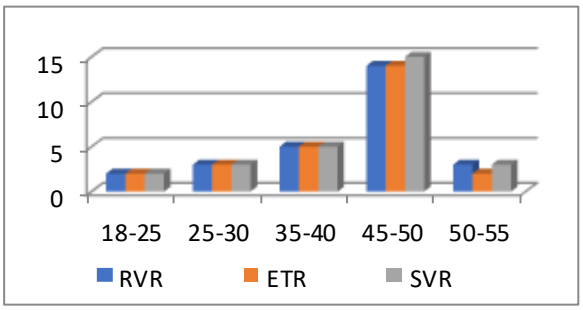
Graph#2: Viral Load in Females



Graph#3: Male treatment response

Table III: Viral load and treatment outcome of female patients					
Age	18-25	25-30	35-40	45-50	50-55
Number of patient	2	4	5	16	4
Viral Load	28175	26543	32175	46532	29674
RVR	2	3	5	14	3
ETR	2	3	5	14	2
SVR	2	3	5	15	3
Relapse	-	1	-	2	1

- RVR achieved: 87.09% (27/31)
- ETR achieved: 83.87% (26/31)
- SVR achieved: 90.32% (28/31)
- Relapsed after SVR:12.9%%(4/31)
- Treatment failure: 22.58%



Graph#4: Female Treatment Response

Table IV: Characteristics of relapsers (Viral load and ALT)						
Age	**Number**		**ALT**		**PCR(viral load)**	
	Males	**Females**	**Males**	**Females**	**Males**	**Females**
25-30	-	1	-	80	-	3485
30-35	1	-	60	-	7453	-
35-40	3	-	72	-	20541	-
45-50	-	2	-	76	-	7432
50-55	-	1	-	112	-	3425
55-60	2	-	48	-	6453	-

The average ALT in male relapsers was 60 whereas that in female relapsers 89.33. No major side effect was noted in males and females. Most common side effect was headache which was noted in 35(26%) of cases and second was body aches with frequency of 14(24%). (Table V)

Table V: The common adverse effects observed in both groups.		
Adverse effects	**Males (69/100)**	**Females(31/100)**
Fatigue	35%	26%
Body aches	14%	24%
Dyspepsia	15%	10%
Headache	10%	20%
Insomnia	18%	13%
Flu like symptoms	8%	7%

The side effects do not require dose reduction of oral sofosbuvir and ribavirin.

Discussion

Sofosbuvir being NS5B, non-nucleotide polymerase inhibitor has pan genotypic effect. The effectiveness of sofosbuvir for different genotypes has been evaluated in different western trails.[10] In eastern countries, GT3 is more prevalent and supportive data is less. Clinical trials conducted on Genotype 3 include Fission, Fussion, Positron, Ally 3 and Boson studies show promising results but require longer duration of treatment.[11-16]

It was shown in Valance Trail that basic problem is to deal with treatment-experienced patients with cirrhosis, SVR in this group was only 60%.[17] It was shown in Boson study that triple therapy of sofosbuvir, ribavirin and pegylated interferon alpha has better results (93%) after 12 weeks as compared to dual therapy in cirrhotic patients. With dual therapy in cirrhotic patients, SVR decreased to 77% and 86% with triple therapy. Triple therapy is of short duration and cannot offered because of adverse effects and poor patient response towards injectables in our society. The combination of sofosbuvir and ribavirin has shown a good safety profile with SVR of 90.32% in females and 88.4% in males with Genotype 3. The haematological and bio-chemical parameters of the patients undergoing treatment do not show significant influence on outcome of treatment. The development DAA has dramatically improved patient tolerability and outcome of treatment. The clinically observed adverse effects are easily manageable.

In our study, the one year follow up reveals a relapse 8.69% in males and 12.9% in females in spite of achieving SVR which require long term follow up of the patients. The overall treatment failure is with sofosbuvir and ribavarin is 22.58% in females and 20.24% in males. Recent strategies are to add additional DDAs to Sofosbuvir include vellpatasvir, daclatasivir or granzoprever plus elbasibivir.[18-20] With an aggressive approach, 90% of reduction in total number of viramic patients is expected by 2030.[21]

The relapse rate of patients, in our study, showed that viral pool in these patients had DDA mutant variant. Different combinations of antivirals with and without pegylated Interferon need to be considered for these patients.

Conclusion

Combination of sofosbuvir and ribavarin is effective in treating genotype 3 naive patients with SVR of 90.32% in females and 88.4% in males. There are few treatment related to adverse effects which need symptomatic management. However, long term follow up is required for relapsers of treatment. The failure of treatment was not very high as per evaluated in the patients.

Acknowledgement

The authors are thankful to the Searle Biosciences, for their support in paper publication. The authors are also thankful to the staffs of Social Security Hospital Islamabad for their support during study.

References

1. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(Suppl 1)-57
2. Attaullah S, Khan S, Ali I. Hepatitis C virus genotypes in Pakistan: a systemic review. Virol J. 2011;8:433
3. Aghemo A, Dore GJ, Hatzakis A, Wedemeyer H, Razavi H. Estimating HCV disease burden - volume 3 (editorial). J Viral Hepat. 2015;22(Suppl 4):1-3
4. Aasld Idsa Hcv Guidance Panel . Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatol. 2015; 62(3): 932-54
5. Ytter FY, Kale H, Mullen KD. Surprisingly small effect of antiviral treatment in patients with Hepatitis C. Ann Int Med 2002;136(4):288-92.
6. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatol 2009;49(4):1335–74.
7. Highlights of prescribing information These highlights do not include all the information needed to use SOVALDI safely and effectively. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM489365.pdf
8. Kattakuzhy S, Levy R, Rosenthal E, Tang L, Wilson E, Kottilil S. Hepatitis C genotype 3 disease. *Hepatol Int.* 2016; 10(6): 861-70
9. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med.* 2014; **370**(21): 1993-2001[DOI][PubMed]
10. Foster GR, Pianko S, Brown A, Forton D, Nahass RG, George J, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. *Gastroenterology.* 2015; **149**(6): 1462-70[DOI][PubMed]
11. Gower E, Estes C, Blach S, Shearer KR, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014;61(1 Suppl):45–57.
12. Mangia A, Piazzolla V. Overall efficacy and safety results of sofosbuvir-based therapies in Phase II and III studies. Dig Liver Dis 2014;46(5):S179–85.
13. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013;368(20):1867–77.

14. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015; 61(4): 1127-35[DOI][PubMed]
15. Foster GR, Pianko S, Brown A, Forton D, Nahass RG, George J, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. *Gastroenterology.* 2015; **149**(6): 1462-70[DOI][PubMed]
16. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med.* 2013; **368**(20): 1878-87[DOI][PubMed]
17. Yu ML, Dai CY, Huang JF, Chiu CF, Yang YH, Hou NJ, et al. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: A randomized trial. Hepatology 2008;47(6):1884–93.
18. A2i2H,Gil ML, Waheed Y ,et al.Evaluation of prog__ factors for peg Interforn alpha-2n plus Interferon on HCV.
19. AKRM M,Idress M,Zafar S, etal. Effect of host and virus related factors on interferon alpha plus ribavirin on HCV Influed patients in Pakistan.Infect Genet Evol 2011;11(3):640-5
20. Farooqi JI, Humayun M, Chaudhry A, Sadik M, Din Z, Alam A, et al. Multi-center experience using Sofosbuvir & Ribavirin with and without pegylated interferon to treat hepatitis C patients with and without liver cirrhosis (RESiP Study: Real-life Experience with Sofosbuvir in Pakistan) [abstract accepted for AASLD 2016 #2548704].