The Professional Medical Journal
www.theprofesional.com

DOI: 10.29309/TPMJ/2020.27.07.3832

ORIGINAL PROF-0-3832

EFFECT OF SOFOSBUVIR BASED ANTIVIRAL TREATMENT FOR ERADICATION OF HEPATITIS C VIRUS ON CLINICAL AND LABORATORY PARAMETERS OF HCV CIRRHOSIS PATIENTS.

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Article received on:
30/04/2019
Accepted for publication:
11/10/2019

ABSTRACT: HCV infects nearly 10 million patients in Pakistan, genotype 3 is the predominant genotype. Liver transplant used to be the only option in patients with decompensated cirrhosis before the emerging role of DAAs. Clinical trials have suggested that successful treatment of HCV in this group results in early improvement in liver function although long term benefit is not yet known. **Objectives:** To measure clinical and laboratory parameter improvement after successful eradication of hepatitis C in cirrhotics. To study any events of decompensation while on treatment. To measure incidence of HCC on/after treatment. **Study Design:** A retrospective, observational study. **Setting:** Fatima Memorial Hospital, Lahore. **Period:** July 2015-April 2017. **Material & Methods:** We included patients with compensated and decompensated cirrhosis with a CTP score ranging from A5 to C12, treated with sofosbuvir and ribavirin or pegylated interferon sofosbuvir and ribavirin. Data analyzed at the initiation, at the end, 12 weeks and 24 weeks post treatment. **Results:** A total of 191 (98 male and 93 female) patients were included in our study. There was statistically significant improvement in albumin, bilirubin, AFP, platelet count, CTP and MELD scores but not in INR. One patient developed ascites and another developed hepatic encephalopathy. Four patients developed HCC during follow up after completion of antiviral therapy. **Conclusions:** 1) Successful treatment of cirrhotic patients leads to improvement in clinical and laboratory parameters. 2) Need for continued surveillance for HCC in patients with cirrhosis remains after successful antiviral treatment.

Key words: Cirrhosis, HCC, Ribavirin, Sofosbuvir, Treatment Outcomes.

Article Citation: Ali B, Ikram Ul Haq R, Alam A, Choudhry A, Nawaz AA. Effect of Sofosbuvir based antiviral treatment for eradication of hepatitis C virus on clinical and laboratory parameters of HCV cirrhosis patients. Professional Med J 2020; 27(7):1371-1376. **DOI:** 10.29309/TPMJ/2020.27.07.3832

INTRODUCTION

HCV infects nearly 10 million patients in Pakistan and it is estimated that approximately 20% of these chronically infected will ultimately progress to develop cirrhosis and death due to end-stage liver disease or hepatocellular carcinoma (HCC).[1,2] Cirrhosis is a debilitating disease especially once decompensation develops.[3] The one year mortality of decompensated cirrhosis is 20%.[4]

The Child-Turcotte-Pugh (CTP) classification has two clinical parameters and three laboratory parameters i.e ascites, portosystemic encephalopathy, total bilirubin, albumin and INR. It has a score ranging from 5 to 15, with a higher score predicting poorer prognosis. Thus the CTP score predicts one and five year mortality in patients with cirrhosis. Owing to the inability of the CTP score to incorporate the additional mortality associated with chronic kidney disease and hyponatremia, MELD and then MELD Na score was developed as predictor of mortality post liver transplant.[5] It now has application in the pre-transplant setting also and allows selection of patients who would be candidates for direct acting antiviral therapy prior to liver transplant. It also allows selecting those patients who cannot undergo a liver transplant.[6]

It has been postulated that with careful selection for treatment, and successful eradication of HCV, the liver function might improve in patients with cirrhosis. This improvement is shown by a decrement in CTP score, MELD score and AFP levels and a rise in platelet count.[7,8] Before

the advent of direct acting anti-virals(DAAs), interferon used to be the only treatment option in combination with ribavirin. Interferon was contraindicated in patients with CTP class B and C cirrhosis.[9] Clinical trials have suggested that successful treatment of HCV in this group results in early improvement in liver function although long term benefit is not yet known.[10]

The objective of this study was to assess the improvement in clinical and laboratory parameters namely CTP and MELD Na scores, AFP and platelet counts in patients with cirrhosis after successful eradication of HCV with sofosbuvir based anti-viral treatment. We also studied any events of decompensation while on treatment and incidence of HCC on/after treatment.

MATERIAL & METHODS

This retrospective, observational study was carried out at Department of Gastroenterology, Fatima Memorial Hospital from July 2015 to April 2017. Approval was taken from the Institutional Review Board (IRB). Consecutive patients presenting to Department of Gastroenterology were enrolled in the study. Inclusion criteria were patients aged between 18 to 65 years and compensated & decompensated hepatitis C cirrhosis as evidenced by a positive HCV RNA by PCR. Amongst these, only patients with CTP score ranging between A5 and C12 with MELD score <18 were enrolled. Treatment naïve and those who had failed previous treatment with interferon (treatment experienced) were included in the study.

Patients with hepatitis B co-infection, HCC or current admission with gastrointestinal bleeding, episode of encephalopathy, spontaneous bacterial peritonitis or hepatorenal syndrome were not enrolled in the study. Those patients who had Chronic Kidney Disease (eGFR <30ml/min) were also excluded. Patients were counseled regarding the study and its implications and an informed consent for participation in the study was taken.

History and examination were carried out when patients were screened for enrollment. Complete blood count, serum creatinine, liver function tests including serum albumin and INR, AFP, HCV RNA by PCR (Qualitative), HBSAg (ELISA) and an ultrasound abdomen were carried out. CTP and MELD scores and eGFR were calculated. Those patients who met the inclusion criteria were treated with sofosbuvir 400 mg once daily and weight based ribavirin (1000 mg/day for<75kg body weight and 1200 mg/day for >75kg body weight) for 24 weeks or pegylated interferon alpha 2a 180 ug once weekly with sofosbuvir and ribavirin (in compensated cirrhosis only with CTP score< 7) as above for 12 weeks as per EASL Guidelines 2015. Once daclatasvir became available in Pakistan patients were treated with sofosbuvir, daclatasvir and/or ribavirin where indicated according to EASL Guidelines 2016. Side effect profile of interferons, sofosbuvir, daclatasvir and ribavirin were explained to the patients and their care-givers in detail.

Once enrolled, patients who were started on the pegylated interferon/sofosbuvir/ribavirin combination were followed up according to the pattern outlined by the EASL guidelines 2015. Patients were asked to present to the Gastroenterology outdoor every two weeks for the first month and then every month for the subsequent two months for the three month regimen that they were on. Patients were examined in detail at every follow-up visit. All potential side-effects of pegylated interferon, sofosbuvir, daclatasvir and ribavirin were inquired about. Note was made of any events of decompensation namely development of ascites, variceal bleeding or portosystemic encephalopathy while on treatment. A complete blood count, serum creatinine, liver function tests including serum albumin and INR were checked at every follow-up visit. Dose adjustment of ribavirin or addition of erythropoietin with closer follow up was advised where hemoglobin fell to less than 8mg/dl.

HCV RNA by PCR (end of treatment response) was also checked at the end of 3 months of anti-viral treatment for those on pegylated interferon/sofosbuvir/ribavirin combination and 6 months of treatment for sofosbuvir/daclatasvir and/or

ribavirin regimen. AFP and ultrasound abdomen was done to rule out HCC for those completing 6 months of sofosbuvir/daclatasvir and/or ribavirin anti-viral treatment and 3 months post treatment for those who had been on a 3 month regimen of pegylated interferon/sofosbuvir /ribavirin.

After 3 months (12 weeks) and 6 months (24 weeks) of completion of antiviral treatment, complete blood count, serum creatinine, liver function tests including serum albumin and INR were checked in both groups. An HCV RNA by PCR (Qualitative) was checked for sustained virological response (SVR12 and 24 respectively.) All this information was carefully recorded on a specifically designed proforma.

All HBsAg negative patients who were never vaccinated against hepatitis B were given complete course of vaccination according to the schedule of 0, 1 and 6 months. Patients were advised to continue surveillance for HCC with AFP level and ultrasound abdomen every 6 months throughout their lives even after successful viral eradication.

We analyzed our data retrospectively at the initiation of treatment, at the end of treatment, 12 weeks and 24 weeks post treatment. Data was analyzed using SPSS and Wilcoxon Signed Ranks Test was applied for two related observations. Mean and SD was calculated for quantitative variables. i.e total bilirubin, INR, serum albumin (components of CTP score), AFP, platelet count, CTP and MELD scores along with age. Frequency and percentages were calculated for qualitative variables i.e sex.

Outcome was recorded in terms of improvement in total bilirubin, serum albumin, INR, platelet count and AFP levels. Similarly, improvement in CTP and MELD scores was also noted. Descriptive statistics were used for development of ascites, portosystemic encephalopathy and variceal bleed which were taken as events of decompensation. Development of HCC in patients on/or after completion of DAAs was also noted similarly.

RESULTS

A total of 191 (98 male and 93 female) patients who had responded to treatment were included in our study. Mean age of the patients was 52.5±9.42 years. Majority of patients were in CTP class A (N142) while N 46 and N 3 patients fell into CTP class B and C respectively.

	Baseline N=191 (M ± SE)	Post Treatment N=191 (M ± SE)	P-Value
INR	1.2 ± 0.0	1.2 ± 0.0	.127
T. Bilirubin	1.2 ± 0.1	1.1 ± 0.1	.000*
Serum Albumin	3.6 ± 0.0	3.7 ± 0.0	.003*
Alpha Fetoprotein	13.1 ± 1.5	8.1 ± 1.5	.000*
Platelet Count	115.0 ± 4.0	124.5±4.7	.000*
CPT Score	6.0 ± 0.0	6.0 ± 0.0	.000*
Meld	9.5 ± 0.2	9.2 ± 0.2	.022*

Table-I.
M=Mean; SE= Standard Error
* Statistically Significant at $p < 0.05$, (Wilcoxon Signed Ranks Test between two related observations)

Results indicated that there was significant (statistically significant at $P < 0.05$ by Wilcoxon Signed Ranks Test between two related observations) improvement in serum albumin, total bilirubin, AFP, platelet count, CTP and MELD scores but no significant improvement in INR (Table-I). Change in CTP and MELD score from baseline shown in Fiugre-1 to 3. One patient developed ascites and the other developed hepatic encephalopathy during treatment and treatment was stopped. Four patients developed HCC during follow up after completion of antiviral therapy, one of them underwent liver transplantation for HCC and recurrence of HCC occurred after 6 months.

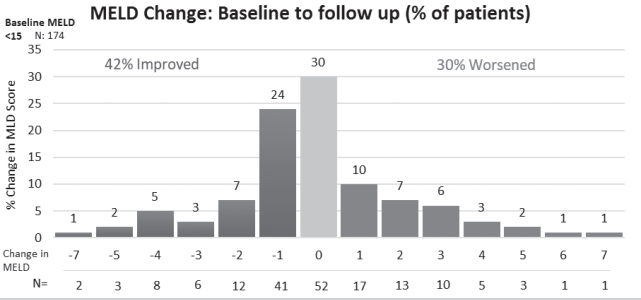

Figure-1

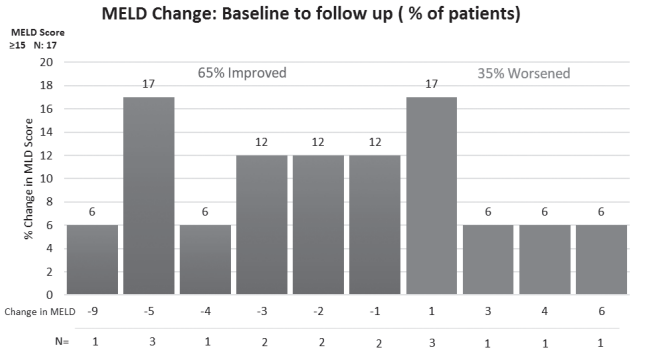

Figure-2

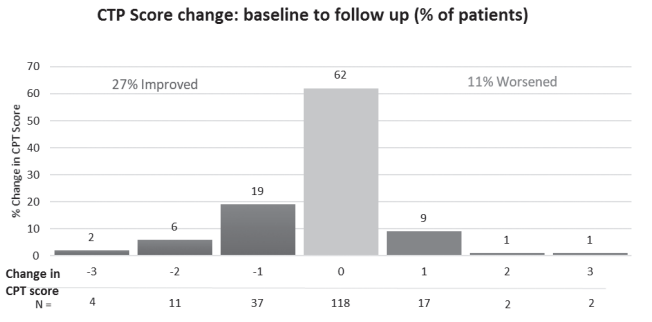

Figure-3

DISCUSSION

The introduction of oral antiviral agents for hepatitis C has opened new doors of hope for patients with liver disease secondary to HCV infection. Patients with advanced liver disease once considered ineligible for therapy, now become eligible after introduction of all oral drugs.[11-14] These drugs not only showed better efficacy against hepatitis C infection but also showed better safety profile as compared to previously used interferon therapy.[15-17]

Patients with cirrhosis, however, pose the greatest challenge as the response rate is still lower as compared to the patients without cirrhosis.[18] The beneficial effects of SVR on patient with advanced liver disease are not completely known. However, few studies showed improved survival after achieving SVR in these patients.[19-22]

We studied improvement in the clinical parameters after successful treatment with direct acting antivirals. There was improvement in total bilirubin levels, serum albumin, platelet count, alpha fetoprotein levels, CTP and MELD scores which is consistent with the study done by Curry et al.[7] Several other studies also showed improvement in MELD score after achieving SVR.[10,23] More improvement seen in the patients with MELD score more equal to or more than fifteen, which is consistent with Curry et al.[7]

There was no significant improvement seen in the INR, It is possible that these parameters may also improve upon long term follow-up. It is important to note that there are also few patients in which there was worsening in MELD and CTP score. What predicts improvement or worsening after antiviral therapy is still to be studied. However a recent study proposed a score, BE3A, which include five Pre-treatment factors (body mass index, encephalopathy, ascites, and serum levels of alanine aminotransferase and albumin) associated with a reduction of Child Pugh Turcotte score to class A in patients with decompensated cirrhosis secondary to HCV infection receiving DAA therapy.[18]

It was encouraging to note that there were only two cases of hepatic decompensation. HCC developed in 4/191 patients which is consistent with the current data on development of malignancy.[24,25] Whether these short term lab and clinical improvements result in improved long term morbidity and mortality remains to be seen and should be a focus of future studies.

CONCLUSIONS

Successful treatment of cirrhotic patients leads to improvement in clinical and laboratory parameters. Careful selection of patients avoids on treatment decompensation with antiviral treatment. Need for continued surveillance for HCC in patients with cirrhosis remains after successful antiviral treatment. Whether these short term improvements result in better long term outcomes remains to be see and should be the subject of future studies.

REFERENCES

1. Mohsin M, Qureshi H. **The first prevalence report on Hepatitis B and C in Pakistan.** Pakistan Journal of Gastroenterology. 2011; 25(1):5-7.

2. Bochud PY, Cai T, Overbeck K, et al. **Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C.** J Hepatol 2009; 51:655-666.

3. Farooqi JI, Alam A. **Hep-net opinion about the management of patients with chronic hepatitis C in Pakistan in the era of available DAA.** J Postgrad Med Inst 2016; 30(1): 6-14.

4. Alexander Z, Guadalupe G, Sebastian R et al. **Prognostic indicators of survival in patients with compensated and decompensated cirrhosis.** Liver Int. 32(9): 1407-1414.

5. Forman LM, Lucey MR. **Predicting the prognosis of chronic liver disease: An evolution from child to MELD.** Mayo End-stage Liver Disease. Hepatology 2001; 33: 473-475 [PMID: 11172352 DOI: 10.1053/jhep.2001.22481]

6. Carrion AF, Khaderi SA, Sussman NL. **Model for end-stage liver disease limbo, model for end-stage liver disease purgatory, and the dilemma of treating hepatitis C in patients awaiting liver transplantation.** Liver Transpl 2016; 22:279–280. doi: 10.1002/lt.24383.

7. Michael P. Curry, Jacqueline G. O'Leary. **Sofosbuvir and velpatasvir for hcv in patients with decompensated cirrhosis.** N Engl J Med 2015; 373:2618-2628

8. El-Sherif, O. and Jiang, Z. (2018). **Baseline factors associated with improvements in decompensated cirrhosis after direct-acting antiviral therapy for hepatitis C virus infection.** Gastroenterology, 154(8), pp.2111-2121.e8.

9. Everson GT, Trouillot T, Trotter J, Skilbred J, Halprin A, McKinley C. **Treatment of decompensated cirrhotics with a low-accelerating dose regimen (LADR) of interferon-alfa-2b plus ribavirin: Safety and efficacy.** Hepatology. 2000; 32:308.

10. Manns M, Samuel D, Gane EJ, et al. **Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 of 4 hepatitis C virus infection and advanced liver disease: A multicentre, open-label, randomised, phase 2 trial.** Lancet Infect Dis 2016; 16:685–697.

11. Lin H, Zeng J, Xie R. **Discovery of a novel 2,6-disubstituted glucosamine series of potent and selective hexokinase 2 inhibitors.** ACS Med Chem Lett 2015; 7: 217-222 [PMID: 26985301 DOI: 10.1021/acsmedchemlett.5b00214].

12. **EASL recommendations on treatment of hepatitis C 2015.** J Hepatol 2015; 63: 199-236 [PMID: 25911336 DOI: 10.1016/j.jhep.2015.03.025].

13. **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].

14. **European association for the study of the liver. EASL recommendations on treatment of hepatitis C 2016.** J Hepatol 2017; 66: 153-194 [PMID: 27667367 DOI: 10.1016/j.jhep.2016.09.001].

15. **Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis.** J Hepatol 2015; 63: 237-264 [PMID: 25911335 DOI: 10.1016/j.jhep.2015.04.006].

16. Friedrich-Rust M, Ong MF et al **Performance of transient elastography for the staging of liver fibrosis: A meta-analysis.** Gastroenterology 2008; 134: 960-974 [PMID: 18395077 DOI: 10.1053/j.gastro.2008.01.034].

17. Staton-Tindall M, Webster JM et al, **Drug use, hepatitis C, and service availability: Perspectives of incarcerated rural women.** Soc Work Public Health 2015; 30: 385-396 [PMID: 25950907 DOI: 10.1080/19371918.2015.1021024].

18. Nelson DR, Cooper JN, Lalezari JP. **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: 1127-1135 [PMID: 25614962 DOI: 10.1002/hep.27726].

19. Davis GL, Alter MJ et al **Aging of hepatitis C virus (HCV)-infected persons in the United States: A multiple cohort model of HCV prevalence and disease progression.** Gastroenterology 2010; 138: 513-521, 521.e1-521.e6 [PMID: 19861128 DOI: 10.1053/j.gastro.2009.09.067].

20. Lacobellis A et al. **Long-term outcome after antiviral therapy of patients with hepatitis C virus infection and decompensated cirrhosis.** Clin Gastroenterol Hepatol. 2011 Mar; 9(3):249-53. doi: 10.1016/j.cgh.2010.10.036.

21. Van der Meer AJ, Veldt BJ, et al. **Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis.** JAMA 2012; 308:2584–2593.

22. Bruno S, Stroffolini T et al Italian **Association of the study of the liver disease (AISF). Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: A retrospective study.** Hepatology 2007; 45: 579-587 [PMID: 17326216 DOI: 10.1002/ hep.21492].

23. Charlton M, Everson GT et al SOLAR-1 Investigators. **Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease.** Gastroenterology 2015; 149: 649-659 [PMID: 25985734 DOI: 10.1053/j.gastro.2015.05.010].

24. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, et al. **Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group.** Inhibition of Hepatocarcinogenesis by Interferon Therapy. Ann Intern Med 1999; 131:174-181.

25. Yang JD, Roberts LR. **Hepatocellular carcinoma: A global view.** Nat Rev Gastroenterol Hepatol 2010; 7:448-458.

AUTHORSHIP AND CONTRIBUTION DECLARATION

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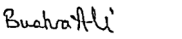
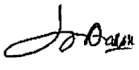
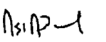
1	Bushra Ali	Principal investigator, study design conception, data collection paper writing with data analysis.	
2	Raja Ikram Ul Haq	Co-investigator, data collection, literature search, paper writing with data analysis.	
3	Altaf Alam	Critical review of article, guidance and supervision in data collection and analysis.	
4	Asad Choudhry	Guidance and supervision in data collection and analysis.	
5	Arif Amir Nawaz	Critical review of article final approval of the work.