

A Randomized study of sofosbuvir plus ribavirin with and without PEG-interferon alpha 2b in treatment of hepatitis C genotype 3 infection: Real life data from a Tertiary Care Center

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Abstract

Background and Aim: Sofosbuvir a polymerase inhibitor is pangenotypic directly acting antiviral for hepatitis C. In this study we evaluate two sofosbuvir-containing regimens either with or without pegylated interferon (PEGIFN) in patients with chronic hepatitis or compensated cirrhosis caused by hepatitis C genotype 3 infection.

Methods: It was a prospective single center randomized open-label study. Thirty-nine patients were randomized into two groups: sofosbuvir plus ribavirin with (A) and without (B) PEGIFN alpha 2b for 12 and 24 weeks respectively. Patients with contraindications and treatment experience were excluded. Primary endpoints were the end of treatment response (ETR) and sustained virological response at 12 weeks (SVR12). Rate of adverse effects was the secondary endpoint.

Results: Baseline characteristics in both groups were comparable. Two patients in group B did not complete therapy and excluded from analysis. ETR and SVR12 rate in group A were 100 % and in group B were 89.4 % showing 100% concordance between ETR and SVR12 in either group. Non-specific adverse effects were more frequent in group A than group B (94.4 versus 79%). Rates of hemoglobin decrease, neutropenia and thrombocytopenia were 100%, 17% and 44.4% in group A and 94%, 0% and 15.8% in group B respectively.

Conclusion: Addition of PEGIFN to sofosbuvir and ribavirin achieves higher ETR and SVR12 and reduces the duration of therapy. PEG-IFN based treatment leads to higher hematological as well as nonhematological side effects but these are mild and easily manageable during 12 weeks treatment.

Keywords: Sofosbuvir, ETR, SVR12.

1. Introduction

Hepatitis C is a common cause of cirrhosis and its complications leading to death worldwide. According to a recent report between 64 and 103 million individuals have chronic hepatitis C infection across the whole world [1]. The prevalence of HCV infection in India is estimated at between 0.5% and 1.5% (15-18 million)[1]. It is higher in the north-eastern part, tribal populations and Punjab areas that may represent HCV hotspots while lower in the western and eastern parts of the country. Genotype 3 is the most common HCV genotype in India (accounting for 54–80% of cases) followed by genotype 1[2]. Combination of

Pegylated interferon (PEGIFN) plus ribavirin was considered standard of care in the treatment of hepatitis C infection a few years back.

Sofosbuvir which is available in India since the first half of the year 2015 is an inhibitor of viral NS5B RNA-dependent RNA polymerase. Sofosbuvir and ribavirin combination for genotype 3 had been evaluated in several studies. A randomized open-label study (ELECTRON trial) [3] evaluated sofosbuvir plus ribavirin with or without PEGIFN in treatment naïve genotype 2 and 3 patients and concluded that sofosbuvir plus ribavirin may be an effective

therapy for genotype 2 and 3 infection. In the FISSION trial in treatment-naïve patients treated for 12 weeks, the SVR rate was 56% (102/183) with better response in the subgroup of patients without cirrhosis (61% and 34% in patients without and with cirrhosis, respectively)[4]. The POSITRON trial included patients who were ineligible or intolerant to PEGIFN-based therapy and treatment was given for 12 weeks with sofosbuvir and ribavirin and SVR was achieved in 61% (60/98) of cases[5]. In the FUSION trial 12 and 16 weeks of therapy was given and SVR was achieved in 30% (19/64) and 62% (39/63) of cases respectively while SVR rate was lower in patients with cirrhosis 19% (5/26) and 61% (14/23) for 12 and 16 weeks therapy respectively [6]. In the VALENCE trial where 24 weeks of therapy was given, the SVR rates were 94% (86/92) in treatment-naïve non-cirrhotic individuals, 92% (12/13) in treatment-naïve cirrhotics, 87% (87/ 100) in treatment-experienced non-cirrhotic patients, and 60% (27/45) in treatment-experienced cirrhotic patients[7]. As per these results 24 weeks duration is the appropriate duration for this regimen in patients infected with HCV genotype 3 and this regimen is suboptimal in treatment-experienced patients with cirrhosis. In these trials combination of sofosbuvir and ribavirin was well tolerated and very few patients stopped therapy.

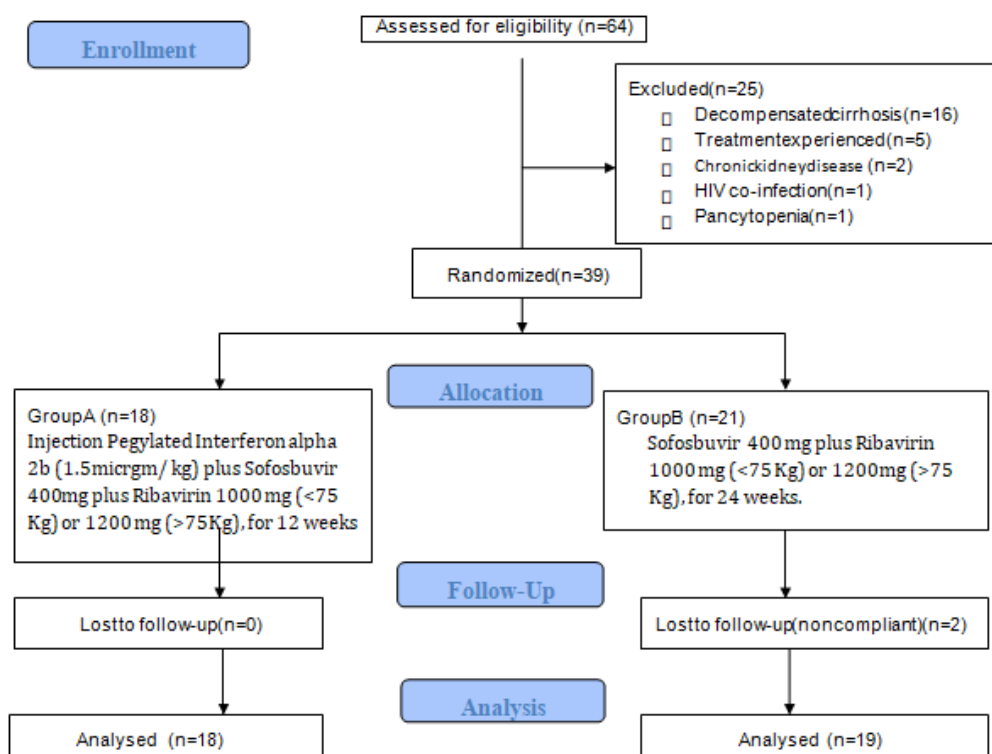
Sofosbuvir and ribavirin in addition to PEGIFN have been evaluated in 10 treatment naïve non-cirrhotic patients infected with genotype 3. Nine of them achieved an SVR, whereas the remaining one was lost to follow-up (PROTON)[8]. In LONESTAR- 2 Phase IIb trial in

genotype 3 treatment-experienced individuals, this triple-drug combination achieved SVR in 83% (20/24) of cases including 10/12 patients with cirrhosis[9]. In another study patients infected with genotype 3 who relapsed after treatment with sofosbuvir and ribavirin retreated with the triple combination of Peg IFN-a, ribavirin and sofosbuvir for 12 weeks achieved an SVR in 91% (20/22) of cases[10]. These results in genotype 3 and pan-genotypic activity of sofosbuvir together with high SVR rates with other genotypes [89% (259/ 291)] overall for genotypes 1 and 4 to 6 indicate that this combination can be safely used in patients infected with HCV genotype 3. SVR rates are lower in treatment-experienced and cirrhotic patients with either of two treatment regimens. With the availability of sofosbuvir in India since 2015 treatment options for genotype 3 included PEG-IFN plus sofosbuvir plus ribavirin, sofosbuvir plus ribavirin and PEG-IFN plus ribavirin. In this study we tend to evaluate two sofosbuvir-containing regimens with or without pegylated interferon in terms of efficacy and adverse events among Indian patients with hepatitis C genotype 3 infections.

2. Study design and methods

It was a prospective, single center, randomized open-label study. Randomization was done by computer-generated random numbers. Informed written consent was taken from all participants. Total 64 patients with hepatitis C infected with genotype 3 infection were evaluated for inclusion in this study over a period of 6 months (April 2017-October 2017) [Figure 1].

Figure 1: Consort flow diagram



Sixteen patients had decompensate cirrhosis, 5 patients were treatment experienced, 2 had concomitant chronic kidney disease, one had low baseline hemoglobin due to tropical splenomegaly syndrome and one was co-infected with human immunodeficiency virus and thus these patients were excluded from the study as per protocol. Total 39 patients were included in the study and randomized into two groups: Group A-Injection PEGIFN alpha 2b (1.5 micrgm/ kg) as subcutaneous injection every week for 12 weeks plus Sofosbuvir 400mg orally once daily for 12 weeks plus Ribavirin 1000 mg (<75 Kg) or 1200 mg (>75 Kg) orally daily in divided dosage for 12 weeks and Group B: Sofosbuvir 400mg orally once daily for 24 weeks plus Ribavirin 1000 mg (<75 Kg) or 1200 mg (>75 Kg) orally daily in divided dosage for 24 weeks.

Patients older than 18 years with hepatitis C genotype 3 virus infections with either chronic hepatitis or compensated cirrhosis were included in the study. Exclusion criteria were signs of decompensation at any time during illness (presence of hepatic encephalopathy, ascites either clinical or on ultrasonography, hepatorenal syndrome, and variceal bleed), history of prior treatment for hepatitis C, autoimmune hepatitis, chronic kidney disease (creatinine clearance <50 ml/minute), co-infection with hepatitis B or human immune-deficiency virus (HBV or HIV), sepsis, severe symptomatic cardiac or pulmonary disease, history of organ transplantation, pregnancy, untreated malignancy limiting survival less than 10 years, uncontrolled psychiatric disorder, uncontrolled seizure disorder, uncontrolled hyperthyroidism or hypothyroidism including autoimmune thyroiditis, baseline Hemoglobin <10 g/dl, baseline neutrophil count < 1500/mm³ and baseline platelet count < 90000/mm³.

Undetectable HCV RNA level at the end of treatment (end of treatment response ETR) and after 12 weeks of completion of treatment (sustained virological response at 12 weeks SVR12) were primary efficacy endpoints. Undetectable HCV RNA at 4 weeks of treatment (rapid virological response, RVR) and incidence of adverse reactions in either group were secondary efficacy endpoints. Patients were followed up every 2-4 weeks for development of any adverse effects to therapy and HCV RNA was done at 4 weeks, at the end of treatment and after 12 weeks of completion of treatment.

2.1 Statistical Analysis

The data collected from OPD /IPD of the gastroenterology department at a tertiary care hospital in north India were entered in Ms-Excel database for the analysis. The data were analyzed by using statistical software SPSS version -16.0. The distribution of patients for continuous variables was represented by Mean \pm St Dev

and for categorical data frequency with their relative percentages was given.

For comparison of quantitative group means student -t test was used and for Qualitative/categorical data Chi-square test was used. A p-value <0.05 was considered as statistically significant.

3. Results

A total 39 patients were randomized in group A (18) and group B (21). In group B one patient stopped treatment after 2 weeks and another was lost to follow up so they were excluded from the analysis of outcomes. Baseline characteristics in both groups were comparable and any difference was statistically insignificant [Table 1].

Evidence of cirrhosis on ultrasonography was present in 39 % (7/18) patients in group A and 48% (10/21) in group B. Upper endoscopy demonstrated varices in 22% (4/18) in group A and 38 % (8/21) in group B. Mean baseline HCV RNA(IU/mL) level in group A was 9.94×10^5 and in group B was 9.30×10^5 . ETR and SVR 12 were seen in all 18 patients in group A (100%) and in 17/19 (89.4%) patients in group B, two of the patients who did not achieve primary efficacy endpoint in group B were cirrhotic. Undetectable HCV RNA at 4 weeks of treatment (RVR) achieved in 94.4 % and 89.4% in both groups respectively [Table 2]. Flu-like symptoms after PEG-IFN injection was seen in almost all patients in group A for initial few injections. Other adverse events like dizziness, anxiety, decreased appetite, body ache, weakness, malaise, headache, and fatigue were non-specific and present more frequently in group A than group B (94.4%, 79% respectively; p-value-0.016).

All patients in group A experienced a fall in hemoglobin from the baseline value, which was also seen in the majority (94%) of group B patients. Mean lowest hemoglobin level during treatment was almost similar in two groups. Treatment modification in form of dose reduction of ribavirin or PEGIFN due to hemoglobin fall needed in 11% patients in group A and 16 % patients in group B (statistically insignificant). The incidence of neutropenia (absolute neutrophil count below 1500/microlitre) was seen in group A only (17% vs 0 %: p-value - 0.06). The incidence of thrombocytopenia (platelet count below 90000/mm³) was significantly higher in group A than group B (44.4 % vs 15.8 %: p-value 0.05). None of the patients in either group required termination of treatment due to development of adverse events. None of the patients in either group developed new-onset thyroid dysfunction or worsening of baseline thyroid function abnormality [Table 3].

Table 1: Baseline characteristics in group A and group B

Parameters	Group A (n=18)	Group B (n=21)	p-value
Mean±SD age-years (Range)	42.2±11.18 (23-3)	47.2±11.51 (20-65)	0.186
Male sex- No. (%)	12 (67)	9 (40)	0.137
Evidence of cirrhosis on USG imaging of liver No.(%)	7 (39)	10 (48)	0.583
Esophageal varix on upper endoscopy - No. (%)	4 (22)	8 (38)	0.284
Hemoglobin (g/dl)- (Mean± SD)	13.1±1.5	12.1±1.4	0.053
Total leucocyte count (Mean± SD)	6700±2320	6667±2155	0.964
Platelet count (mean± SD)	165000±67789	151000±52379	0.473
Random blood sugar (mg/dl) (Mean± SD)	95.3±12.7	105.6±20.7	0.070
Aspartate Aminotransferase (IU/dl) (Mean± SD)	105.6±130.9	105.3±64.3	0.994
Alanine aminotransferase(IU/dl) (Mean± SD)	90.2±58.6	81.6±53.0	0.595
Albumin(g/dl) (Mean± SD)	3.9±0.6	3.6±0.8	0.107
Creatinine(mg/dl) (Mean± SD)	0.80±0.19	0.88±0.15	0.131
HCV RNA(IU/mL) x10 ⁵	9.94±1.35	9.30±1.31	0.882
Thyroid abnormality at baseline No.(%)	2 (11)	1(5.2)	0.515

Table 2: Virological responses

Parameters	Group A (n=18)	Group B (n=19)	p-value
Rapid virological response at 4 weeks- No.(%)	17(94.4)	17 (89.4)	0.579
Early virological response at 12 weeks -No (%)	18 (100)	17 (89.4)	-
End of treatment response- No.(%)	18 (100)	17 (89.4)	-
Sustained virological response 12 weeks after end of treatment	18 (100)	17 (89.4)	-

Table 3: Rates of adverse events in two groups

Parameters	Group A (n=18)	Group B (n=19)	P value
Hemoglobin (Hb) fall during treatment - No. (%)	18(100%)	16 (84%)	-
Lowest Hb during treatment (Mean±SD)	10.7±1.2	10.4±1.7	0.636
Treatment modification due to Hb fall- No (%)	2 (11%)	3 (16%)	0.677
Neutropenia during treatment - No (%)	3 (17%)	0 (0%)	0.063
Thrombocytopenia during treatment - No (%)	8(44.4%)	3(15.8%)	0.056
Overall incidence of clinical side effects - No (%)	17(94.4%)	15(79%)	0.0168
New onset thyroid abnormality - No (%)	0(0)	0(0)	-

4. Discussion

Sofosbuvir a pangenotypic DAA is an analog of the pyrimidine nucleotide uridine and inhibitor of viral NS5B RNA-dependent RNA polymerase. It is a prodrug that undergoes intracellular metabolism in the hepatocytes to its active form, GS-461203, which acts as a chain terminator [11-13].

The inclusion of sofosbuvir in treatment armamentarium of hepatitis C has dramatically increased SVR rates for all genotypes but this increase is less profound for genotype 3 infections. Sofosbuvir and ribavirin combination has been recommended by major liver study groups for genotype 3 infection until availability of daclatasvir which when combined with sofosbuvir results in excellent SVRs. Sofosbuvir and ribavirin along with PEGIFN for 12 weeks lead to 95% and 91 % SVR rate in treatment naïve and experienced patients (BOSON trial)[14].

In our study, 100 % patients in group A (PEGIFN based) achieved primary efficacy outcomes (ETR and SVR12). Correlation between ETR and SVR 12 was 100 % in our study which is an important finding in patients

treated with DAAs based regimen. High SVR rates in patients with genotype 3 infection with PEGIFN based sofosbuvir containing regimen is consistent with other trials too like PROTON [8] (n=10; SVR12 90%) and ELECTRON[3] in treatment naïve patients. SVR 12 rates were similar in both cirrhotic patients and non-cirrhotic patients with this regimen. Outstanding response to this regimen promisingly holds ground for it in treating genotype 3 infections in India.

Overall lower ETR/SVR12 rates were seen with sofosbuvir and ribavirin combination only for 6 months and both non-responders were cirrhotic concluding that this regimen is inferior to PEGIFN based regimen for 12 weeks in cirrhotic patients. With the availability of daclatasvir in India treatment of patients with genotype 3 infection is much easier with sofosbuvir plus daclatasvir regimen than PEGIFN based regimen. Still, PEGIFN and sofosbuvir based regimen can be considered the second option for these patients and first option for those who were non-responder to sofosbuvir plus daclatasvir regimen.

Hematological side effects were higher in group A patients but were easily managed and didn't lead to

termination of therapy. Hemoglobin fall in group A could be due to combined effects of bone marrow suppression by interferon and hemolysis by ribavirin.

The high rate of hemoglobin reduction was seen in group B also and this could be due to prolonged (6 months) therapy with ribavirin as it is known to cause dose-dependent hemolytic anemia. Nonspecific side effects like dizziness, anxiety, decreased appetite, body ache, weakness, malaise, headache, and fatigue were significantly higher in group A than group B patients (p value-0.016). One drawback as seen in this study with all oral regimen sofosbuvir plus ribavirin was that 2/21 (9.5%) patients were lost to follow up after the start of therapy. Being an open-label study selection bias cannot be ruled out completely. Another limitation was limited number of patients enrolled in this study at a single center.

5. Conclusion

PEGIFN with sofosbuvir and ribavirin for 12 weeks achieves higher ETR and SVR12 rates as compared to sofosbuvir and ribavirin for 24 weeks in treating patients infected with hepatitis C genotype 3 in India. PEGIFN based regimen is superior to PEGIFN free regimen in patients who have cirrhosis in particular. This interferon-based regimen has higher hematological as well as nonhematological side effects in comparison to sofosbuvir and ribavirin but they are mild and easily manageable. Though enrolled a small number of patients, data can be used from this study to further explore the role of PEGIFN and sofosbuvir containing regimen in larger studies for treating genotype 3 infections in India.

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Conflict of interest: Authors have none to declare.

References

- [1]. Hatzakis A, Chulanov V, Gadano AC, et al. The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm – volume 2. *J Viral Hepat.* 2015; 22(suppl. S1): 26–45.
- [2]. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology.* 2015; 61: 77–87.
- [3]. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med.* 2013; 368: 34–44.
- [4]. Reyes-Mendez MA, Juarez-Figueroa L, Iracheta-Hernandez P, Medina-Islas Y, Ruiz Gonzalez V.

Comparison of two diagnostic algorithms for the identification of patients with HCV viremia using a new HCV antigen test. *Annal Hepatology.* 2014; 13: 337–342.

- [5]. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med.* 2013; 368:1867–1877.
- [6]. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med.* 2013; 368:1867–1877.
- [7]. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med.* 2014; 370: 1993–2001.
- [8]. Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peg interferon alfa2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomized, double-blind, phase 2 trial. *Lancet Infect Dis.* 2013; 13:401–408.
- [9]. Lawitz E, Poordad F, Brainard DM, et al. Sofosbuvir in combination with Peg IFN and ribavirin for 12 weeks provides high SVR rates in HCV-infected genotype 2 or 3 treatment-experienced patients with and without compensated cirrhosis: results from the LONESTAR-2 study. *Hepatology.* 2013; 58:1380 A.
- [10]. Esteban R, Nyberg L, Lalezari J, et al. Successful retreatment with sofosbuvir-containing regimens for HCV genotype 2 or 3 infected patients who failed prior sofosbuvir plus ribavirin therapy. *J Hepatol.* 2014; 60: S4.
- [11]. Bourlière M, Khaloun A, Wartelle- Bladou C, et al. Chronic hepatitis C: treatments of the future. *Clin Res Hepatol Gastroenterol* 2011; 35: Suppl 2: S84-S95.
- [12]. Lam AM, Murakami E, Espiritu C, et al. 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: 3187-96.
- [13]. Sofia MJ, Bao D, Chang W, et al. Discovery of a β -d-2'-deoxy-2'- α -fluoro-2'- β - Cmethyluridine nucleotide prodrug (PSI- 7977) for the treatment of hepatitis C virus. *J Med Chem* 2010; 53:7202-18.
- [14]. Foster GR, Pianko S, Brown A, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with HCV genotype 3 infection and treatment-experienced patients with cirrhosis and HCV genotype 2 infection. *Gastroenterology.* 2015. <http://dx.doi.org/10.1053/j.gastro.2015.07.043>.