Sorafenib tosylate, Ribavirn and Sofosbuvir combination therapy for HCV virus infected patients with decompensated liver cancer

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Abstract: Hepatitis C is the most common health problem worldwide and is major cause of death due to proliferation of hepatocellular carcinoma. The medicines available for HCV treatment overcome up-to 95% complications of HCV. However, liver cancer needs some additional care. Normally Sorafenib tosylate 200 mg is recommended for liver cancer. There is no such trial in which this drug could effectively be used in combination of direct acting antivirals for HCV. The study was conducted for HCV patients (n=30) with liver cancer having decompensated stage. Combination of Sorafenib tosylate, Ribavirn and Sofosbuvir were used for the pharmacokinetics of these medicines. Child pugh score less then 7 (CP A) in adults during treatment phase (received 12 weeks of Sorafenib tosylate 200 mg, Ribavirn and Sofosbuvir 400 mg once daily) have no side effect while child pugh score 7-9 (CP B) have evidence of hypertension. The main efficiency end point sustained virology response with overcoming liver cancer as well in 12 weeks after end treatment (SVR-LLC 12). Mean pharmacokinetic exposure to Sorafenib tosylate 200 mg, Ribavirn and Sofosbuvir at week 8th was 2.1, 1.5,1.2 times greater in CP B than in CP A. Adverse effects (AEs) were observed in 12 out of 30 patients but not severe as lethal for life. Treatment with Sorafenib tosylate, Ribavirn and Sofosbuvir for twelve weeks was harmless and well accepted, 100 % patients achieve (SVR LLC 12) with 10-fold cure rate more than previous ones. The combination therapy of Sorafenib tosylate, Ribavirn and Sofosbuvir was found helpful for the management of decompensated liver cancer.

Keywords: Child pugh (CP), sustained virologic response (SVR), adverse effects (AEs).

INTRODUCTION

HCV is the main cause of death in humans over the years. There is no vaccine available for the prevention of HCV. However, treatment success rate has been enhanced up-to 90% with recent advancement in therapy (Charlton *et al*., 2015). Different strategies have been adopted for viral clearance and management of symptoms. Interferon therapy in combination with ribavirin has been extensively used but the success rate was low. Relapse of viral attack was another risk for health of infected person as HCV disguised himself in hepatocytes for long time.

Recently, direct acting antiviral drugs (DAA) have shown promising results to get rid of HCV. The oral use of these drugs has further facilitates the treatment along with combination therapy (Ferenci, 2015). These drugs overcome up-to 95% complications of HCV however, liver cancer need some additional care and medication (Foster *et al*., 2016). Sofosbuvir is direct acting antiviral drug for HCV treatment. This pro drug is metabolically activated to form uridine triphosphate analogue to be incorporated into non-structural (NS5B) part of HCV genome having polymerase activity (Amico *et al*., 2006, US Food and Drug Administration 2010). Normally Sorafenib tosylate 200 mg tablet is recommended for liver cancer however, there is no such trial available so that this drug could effectively be used in combination of direct acting antivirals for effective overcome on complication of HCV (Kwo and Badshah 2015, Nazario *et al*., 2015, Mannas *et al*., 2016). The combination therapy may increase the cure rate especially in patients having end stage liver disease. Pharmacokinetics of these medicines will highlight the effectiveness to protect liver cirrhosis and possible adverse effects of this combination therapy against HCV and management of liver cancer.

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MATERIALS AND METHODS

Study design and patients

This study was designed specifically for the improvement of cure rate of hepatocellular carcinoma caused by HCV. The study period started from September 2016 in Faisalabad, Punjab, Pakistan. Ethical review committee of Government College University Faisalabad approved said study as it meets with the principle of the declaration of GCUF. Written informed consents were taken from all patients and those participating willingly, were selected for further study. Adult patients (≥18 years) with chronic HCV were included in this study. The HCV RNA virus count was evaluated by quantifying RNA level > 10,000

IU/mL at the time of selection and cirrhosis was confirmed through fibro scan. Combination therapy recommended by the physicians (liver center DHQ hospital, Faisalabad) included antiviral drugs for HCV and drug for liver cirrhosis as well. The patients were divided into two groups depending upon severity and status of liver disease by CP score. Panel 1had a CP score <7 with documented portal hypertension and gastroscopy esophageal veins and hepatic venous pressure gradient ≥10 mmHg; Child Pugh score 7-9 was documented for Panel 2 (fig. 1). The patients previously treated with anti-HCV treatment at any stage were excluded from the study. The experimental design consisted of three phases: First, selection stage of almost 4 weeks; Second, open labeled treatment phase for 12 weeks and; Third, post treatment follow up for 12 weeks. Patients received Sorafenib tosylate 400 mg, Ribavir 400 mg and Sofosbuvir 400 mg QD for 12 weeks.

Procedure

Blood samples were collected at predefined time intervals for the quantitative analysis of HCV RNA level in patients. COBAS ampliprep/COBAS Taq-Man Quantitative test for HCV V2.0 (Lower limit of quantification=Limit of detection=15 IU/mL) was used for the measurement of HCV level in patients (Pawlotsky *et al*., 2015). HCV NS3A, NS4A, NS5B and NS5A sequencing was performed before treatment in all patients for the identification of existing sequence polymorphism. Model for end stage liver disease was used for the detection of liver disease. Fibro test and fibro scan scores were measured at either screening time or zero time and during follow-up and changes over time in CP and MELD scores for baseline to follow up. Before the experimental stage pharmacokinetic data were collected. Adverse events throughout the treatment and follow up periods were also recorded (table 1).

Outcomes

The primary effectiveness endpoint was SVR 12 (HCV RNA level ≤15 IU/mL for detectable or non-detectable 12 weeks after actual EOT) in the target population (patients received at-least one dose of the medicine). The following key points were recorded SVR rate after four weeks of EOT, SVR rate after 24 weeks of EOT, by the virology response on treatment (HCV RNA ≥15 IU/mL detectable or non-detectable at all time points); Failure of treatment with viral brake-through (confirmed >1.0 log10 increase in HCV RNA from established HCV RNA >100 IU/mL in patients achieving HCV RNA <15I U/mL on- treatment); viral reload (patient not achieved SVR12, having non-detectable RNA level at EOT and having definite RNA ≥15 IU/mL during the follow- up); The patients not achieving SVR12 and changed baseline sequence in HCV NS3A, NS4A, NS5A and NS5B, PK parameters for Sorafenib tosylate, Ribavirn, Sofosbuvir, safety and tolerability, end point and the treatment effect on liver disease.

STATISTICAL ANALYSIS

This study was exploratory so there was no need of sample size calculations. Twenty patients were selected per panel which based on SVR level having 95% confidence interval level both sides and confidence intervals (CIs) with sufficient precision (Appendix S1) ITT population were used for the performance of all efficacy analyses. Descriptive statistics used for the primary, secondary and exploratory endpoints. The Non-compartmental PK analysis was performed and data for safety measures was descriptively analyzed. Results were presented by using basic statistics tools.

RESULTS

Patients

Initially 50 patients were pre-selected for this study, out of which 30 were enrolled finally including 18 in CP A and 12 in CP B group. Demographic data of the selected patients is given in table 1. CP A group male (63%) and female (37%) patients showed non compensated IL28B genotyping (83%), of higher Body Mass Index (>28.5) and (upper gastrointestinal varices indicates portal hypertension in 100% patients. Mean baseline score 10.01% was detected in CP B patients and 95% patients shows clinical symptoms of (ascites, 81%; hepatic encephalopathy, 65%; median albumin, 3.3 g/dL). Low level resistance in a naturally occurring polymorphism of baseline NS3 Q80K, in 9 out of 18 GT1A infected patients was observed for Simprevir from available sequence data. Table 1 presents all baseline Sorafenib tosylate, Ribavirn and Sofosbuvir resistance- associated variants. Only a single patient (1/30, 3%) had both Ribavirn and Sofosbuvir RAVs at baseline (Q80R in NS3 and Y93H in NS5A). In addition, 2 of 30 (5%) patients had Sorafenib tosylate RAV Y93H at baseline. S282T with Sofosbuvir resistance was never seen at baseline (table 1).

Pharmacokinetics

The PK exposure at 8th week (maximum plasma concentration of dosing and area under curve over the dosing intervals [AUC24h]) to Sorafenib tosylate, Ribavirn and Sofosbuvir was 2.1-, 1.5-, 1.2- times greater in patients with CP B than in CP A.

Safety

No severe adverse effect (AE) or death occurred during the treatment phase to discontinue therapy. Grade ½ AEs were reported during treatment phase in 20/30 patients. Only one patient had AEs 3 (gastrointestinal hemorrhage) in CP B group during 6th week of therapy. This life threatening AE was not due to this combination therapy (table 2). The most common AEs reported were urinary track abstraction, photosensitivity, irritability, hepatic encephalopathy, anaemia and insomnia (table 2). During

Table 1: Demographic parameters of the patients receiving combination therapy of Sorafenib tosylate, Ribavirn and Sofosbuvir

Demographic parameters	CP A (n=18)	CP B (n=12)	Total (n=30)
Median age (Years range)	56 (30-64)	61 (50-75)	58.5 (30-75)
Male n %	14(74)	11(52)	25(63)
BMI, median (range)	26.8 (22.7- 35.5)	31.8 (21.2- 47.0)	28.5 (21.2- 47.0)
Baseline HCV RNA (log10 IU/mL), median (range)	5.8 (4.8- 6.8)	5.6 (4.0- 6.7)	5.7 (4.0- 6.8)
PR- treatment- experienced, n (%)	9(47)	10(48)	19(48)
HCV GT, n (%)			
With NS3 Q80Kb	9 (60)	3(30)	12(48)
3a	16	10	26
1a	2	2	4
IL28B non- CC, n (%)	15(89)	10(72)	25(89)
Median FibroScan® score, kPa (range)	21.8 (14.9-43.5)	30.8 (20-42)	27(14.9-75)
MELD score, n (%)			
<10	12(63)	6(48)	18(55)
≥10- <15	5(26)	5(13)	10(39)
≥15	1	1	2
CP score, n (%)			
5	14(73)	0	14
6	0	6	6
7	0	9	9
8	0	8	8
9	0	4	4
Albumin (g/dL), median (range)	4.2	3.2	3.9
Bilirubin (mg/dL), median (range	1.00	1.5	2.5
Platelets ($\times 10^3/\mu L$), median (range	106	79	79.5
Hepatic encephalopathy, n (%)	3(15)	6(25)	9(40)

GT 3a) calculated with GT a3 infected patients with available sequenced data
GT1a) calculated with GT a1 infected patients with available sequenced data

the treatment phase of this study, 0 of 18 CP A patients have seen adverse effects and 2 of 12 CP B (10%) patients have some clinical symptoms of jaundice and bleeding from the intestine. These patients also have history of esophageal bleeding.

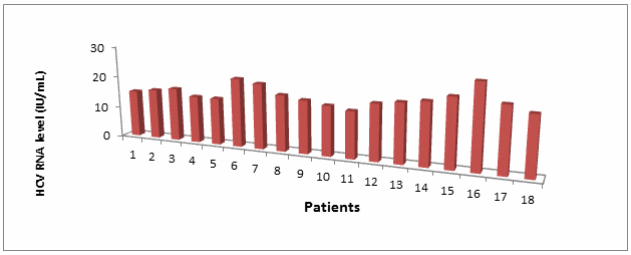

Fig. 1: HCV RNA levels in CP A patients. CP A patients 18/18 (100%) for available data of week 4 had HCV RNA level <15 IU/mL.

DISCUSSION

All treatment options for patients who received this treatment either they had liver cirrhosis or hypertensions CP A or they had decompensated liver CP B almost 100% achieved SVR 12 or SVR 24 even in some cases presence of RAVs at baseline. After one month of successful therapy, all patients of CP A (100%) and 10 out of 12 patients of CP B (83%) had HCV RNA level <15 IU/mL (detectable or non-detectable). The viral clearance rate was very slow in CP B patients however, the recovery from liver cirrhosis was achieved at SVR12 so it indicates that treatment outcomes may be poorly described on the base of early viral dynamics (Ouwerkerk *et al.*, 2015, Pockros *et al*., 2016). This impact of study describes 100% achievement of SVR 12 with Sorafenib tosylate, Ribavirn and Sofosbuvir however, without presence of Sorafenib tosylate (control group) have very less efficacy against CP B, decreased SVR rates after the successful therapy for 12 weeks. For ASTRAL-4 investigations combination therapy including Sofosbuvir, Ribavirin with Sorafenib tosylate was performed in patients with decompensated liver stage and overall therapy for SVR12 indicated that 95% CP B cases recovered without any further complication. However, there is need of some more wide area research and investigation for the proper pharmacokinetic mechanism of Sorafenib tosylate, Sofosbuvir and ribavirin. The decompensated liver cirrhosis, OPTIMIST- 2 study, data identify that HCV genotype GT1A have numerically low value of SVR 12 (Samonakis *et al.*, 2014). The patients having starting point NS3A, B Q80K polymorphism when compared

Table 2: Adverse events during the treatment of HCV with combination therapy and grade three and four treatment emergent laboratory irregularities (ITT population).

AE n %age	CP A (n=18)	CP B (n=12)	Total (n=30)
Any AE	11	12	23
Grade 1 or 2	11	11	22
Grade 3 or 4	0	1	1
Deaths	0	0	0
Early discontinue due to AE	0	0	0
Treatment- related AEs			
Due to Sorafenib tosylate possibly	2	4	6
Due to Ribavirn	1	1	2
Due to Sofosbuvir	0	1	1
AEs in ≥2 patients			
Urinary tract infection	1	2	3
Photosensitivity reaction	2	1	3
Nausea	1	2	3
Hepatic encephalopathy	0	2	2
Anaemia	0	2	2
Grade 3 or 4 treatment- developing laboratory abnormalities bilirubin b,c,d	2	1	3
Grade 3	0	0	0
Grade 4	1	2	3
Glucose elevations	2	2	4

Not relevant to treatment of said study. B
12 weeks follow-up shows normal Bilirubin value
There was no prominent abnormality seen for transaminase. D Bilirubin and Grade three total Bilirubin increase: >2.5- ≤5.0×ULN; Grade 4 total bilirubin increase: >5.0×ULN.

HCV infected patient of GT1A devoid of having such polymorphism (74% v/s 92%) (Westbrook and Dusheiko 2014, Stedman, 2014). However, in this research it was described that there was no effect of Q80K polymorphism on SVR 12. The study suggested that the addition of Sorafenib tosylate in Ribavirn/Sofosbuvir regimen was most successful therapeutic option for patients having end stage of cirrhotic liver. Liver function in the patients who achieved SVR12 was improved due to the addition of anti-cancer drug with antiviral agents.

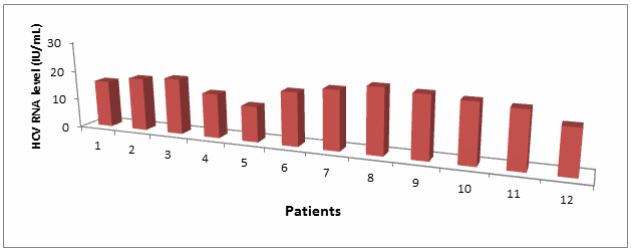

Fig. 2: HCV RNA levels of CP B patients. CP B patients, 11/12 (90%) had HCV RNA <15 IU/mL at week 4.

The data also revealed that CP and MELD scores were improved and stabilized from baseline to SVR12 and in 12 weeks follow-up period also. The one year follow up plan will further provide insight information regarding outcomes of this combination therapy for end stage liver disease where survival rate was very low without the combination of this therapy. It was also observed that Lower level of Cytochrome P450 and expression of drug transporter was correlated with progression of this disease resistance (Saxena *et al*., 2015, Sofia, 2015, Poodad et al., 2016).

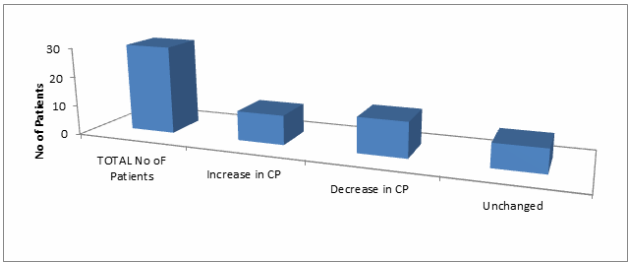

Fig. 3: CP score decreased in 12 patients and increased in 10 patients and remained unchanged in 8 patients.

The bilirubin level was increased in the patients of CP B group which may lead to jaundice. However, there is a need of care in the use of protease inhibitors which may lead to liver toxicity and non-functionality. A recent study highlighted the scenario that Grazoprevir which is NS3A and NS4A protease inhibitor when given with Elbasvir which is NS5A and NS5B replication complex inhibitor for the treatment of GT1 infected patients of HCV having CP B shows slightly greater plasma level of Grazoprevir in patients who received 50 mg and have cirrhosis as compared with patients who receive 100 mg but have no cirrhosis. There was no dose dependent effect seen for this

therapy as CP B patients shows SVR 12 with 90% success rates. Overall, these two direct acting antiviral drugs along with anticancer medicine showed promising results and have more accuracy especially in patients having liver cirrhosis (Kwo and Badshah 2015).

CONCLUSION

The combination therapy for HCV viral infected patients along with liver cancer therapy with Sorafenib tosylate, Ribavirn and Sofosbuvir showed promising results for the treatment of liver cancer along with the clearance of HCV viral load. This study was on limited number of patients so it may be further elaborated for more accuracy.

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