Original Article

Efficacy of Sofosbuvir and Ribavirin for Treatment of Chronic Hepatitis C Genotype 3 Treatment Naïve Non-Cirrhotic Patients at KGN Teaching Hospital Bannu

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ABSTRACT

Objective: to assess the efficacy of oral sofosbuvir and weight-based ribavirin treatmentin non-cirrhotic treatment-naïve patients in district Bannu, Pakistan.
Study Design: A quasi-experimental study
Place and Duration of Study: This study was conducted at the Khalifa Gul Nawaz Teaching hospital (KGNTH) Bannu from June 2016 to January 2018.
Materials and Methods: 340 patients having GT 3 which were non-cirrhotic and treatment naïve. Non-probability consecutive sampling technique was used for sample collection. Treatment was given to all subjects with sofosbuvir (400mg)OD with weight-based ribavirin BD for a period of 24 weeks. PCR was done for follow up at the end of treatment (ETR) and at completion of week 12 of treatment in order to determine virologic response (SVR).
Results: 96.25% (n=318) of the patients had achieved negative PCR at the end of treatment. SVR 12 was achieved in 92.78% (n=306) of subjects in which 84.00% (n=260) had negative PCR. 35.55% (n=117) had Hemoglobin reductions below 10.0g/dl during the treatment course. Females population was found with a sustained virologic response a little more (p=0.003)
Conclusion: Sofosbuvir and RBV based regimen is an effective treatment option for patients in treatment naïve non-cirrhotic GT3 patients with good tolerability and fewer side effects as compared to previous interferon-based regimens. Our results suggest the feasibility and the pertinence if including interferon-free treatment regimens in the national programme, at both provincial and national levels.
Key Words: HCV, Sofosbuvir, Genotype 3, PCR, Hepatitis C, Ribavirin

INTRODUCTION

Hepatitis C is a persistent viral infection of the liver, if left untreated will result in major medical morbidities i.e. cirrhosis, hepatocellular carcinoma and their sequelae. Hepatitis C Virus (HCV) infection is a significant global health burden with approximately 160-180 million infected which accounts for 1% of world population. [1]Six known genotypes of hepatitis c exist, with genotype 1 predominance in USA and Europe.

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Patients who develop cirrhosis and hepatocellular carcinoma result in ~350,000 estimated deaths from these complications annually.[2] Pakistan is ranked second around the globe with high a prevalence 4.9%.[3] Pakistan is a lower middle-income country with a population of approximately 220 million.Most important risk factors for HCV transmission in Pakistan are health system-related, including a documented high frequency of therapeutic injections, reuse of syringes, and unlicensed clinics conducting high volumes of blood transfusions, dental surgeries[4] . In one study, most HCV infections in Pakistan are genotype 3 (69.1%), followed by genotypes 1 (7.1%), genotype 2 (4.2%) and genotype 4 (2.2%).[5,6] In another study, genotype 3 accounts for around 90% .[7]
GT 3 is the second most common HCV genotype globally, accounting for 18%of all adult HCV infections. Patients with HCV GT3 infection have greater risk of developing hepatic steatosis, more rapid progression of hepatic fibrosis and cirrhosis and hepatocellular carcinoma. GT3 is less responsive to interferon-based treatment.

New direct acting anti-viral oral regimens (DAAs)have revolutionized management of chronic hepatitis C since 2011, with ease of administration and fewer serious side effects. Since the launch of DAAs, sustained virologic response was nearly 100% with exception to GT 3 which is associated with lower SVR rates [8].sofosbuvir and ribavirin regimen became available in Pakistan by November 2014[9-13].Limited data was available from the clinical trials regarding the response of DAAs in GT3 patients in real-world. Based in Asian Pacific Association for the Study of Liver Disease (APASL) 2016 guidelines, recommended therapies for GT 3 include:

1) Sofosbuvir + weight-based Ribavirin (RBV) treatment for 24 weeks for treatment naïve patients
2) Sofosbuvir+ Daclatasvir for 12 weeks in patient without cirrhosis and 24 weeks with or without weight-based ribavirin with cirrhosis
3) Among those with treatment experienced – interferon based, Sofosbuvir+ Daclatasvir for 12 weeks in non-cirrhotic and Sofosbuvir+ Daclatasvir with weight based Ribavirin for 24 weeks with cirrhosis [14]

Since the introduction of DAAs, real world effectiveness results have been sporadically published with considerable heterogeneity. Bannu is the district of KP, in 2017 census had a population of 9,58,000. It is located in the southern part of Khyber Pukhtunkhwa.[13]

To gain real-world data on effectiveness in local population of Bannu, Sofosbuvir+ weight-based Ribavirin was given to all GT 3, non-cirrhotic patients for 24 weeks and studying SVR12.

MATERIALS AND METHODS

This study (quasi experimental) was conducted at Khalifa Gul Nawaz teaching hospital (KGNTH) Bannu for a period of 24 months. Protocols for the use of laboratory animals were in accordance with the guidelines of the BMC ethical board. All patients with chronic HCV infection (either diagnosed with HCV in our hospitalor those referred for HCV treatment from other institutions), were confirmed through baseline quantitative PCR (real time assays) followed by determination of genotype using single noucleotide polymorphism (SNP).Previous treatments for Hepatitis C was evaluated by taking proper history and going through patients documents and patients with no confirmed past exposure to any anti-HCV treatment were separated. Treatment naïve genotype 3 patients were then included in study and assessed for cirrhosis status using Child Pugh scores, ALT and hepatobiliary ultra sound study to rule out cirrhosis and hepatocellular carcinoma. Patient with age18 years or more, having no cirrhosis or child pugh score less than 5 and genotype 3were started on treatment with daily oral sofosbuvir 400mg and ribavirin (weight-based) for 24 weeks. A total of 340 patients got enrolled in the study during the said duration. Patients were counselled concerning the disease, compliance with treatment and lifestyle changes including family planning. 60.00% (n=204) of patients were male while 40.00% (n=136) were female.

Inclusion criteria

- Patients having an age above or 18 years
- Male and female
- Treatment naïve
- Non-cirrhotic with child pugh<5, ultra sound study negative for cirrhosis /HCC
- GT3 mono infected patients

Exclusion criteria

- Previous anti HCV treatment experienced patients
- Acute HCV infection
- Patients with cirrhosis child pugh score>5 or hepatocellular carcinoma
- Patients with HIV/HBV co-infection
- Patients on treatment for tuberculosis and chemotherapy
- Patients eligible for treatment but not willing to undergo family planning.
- Patients below 18 years old.
- Pregnant patients and lactating mothers."

Treatment outcomes definition

- End of treatment (ETR) response: An undetected HCV RNA by PCR at 24 weeks completion of treatment.
- Sustained Virological Response (SVR) 12: Absence of viremia 12 weeks post treatment as evidenced by a negative HCV RNA Quantitative PCR.
- Relapse: Recurrence of viremia at 12 weeks post treatment after aundetected end of treatment viral load.
- Non-responder/ Treatment failure: Persistence of viremia at the end of treatment i.e. 24 weeks
- Stopped treatment: Medical decision to stop treatment either from complications of treatment or from decompensation. Patients are referred to dedicated liver centre for further management. No viral load is taken after stopping treatment.
- Lost-to-follow-up: Patients who missed follow-up consultation at least 60 days from the appointed date, despite tracing efforts. Died: Patients who died while enrolled to the programme

Treatment duration was 24 weeks. Sofosbuvir was administered orally 400mgOD. RBV was given (<75kg 1000mg and >75kg 1200 mg daily) in two divided doses. During treatment, patients were asked to come for follow-up check upevery month for medications refill, clinical examination and laboratory assessment with complete blood couts, ALT, AST, assessment of compliance to family planning advice and lifestyle counseling sessions by attending physician. At the end of treatment, viral load was measured using real time

PCR assay. A second viral load was done twelve weeks after treatment completion to determine the sustained viral response (SVR).

Study Design: Open label, quasi experimental study design (single group study lacking any control group).

Variables and analysis Data from the Hepatitis C database were used to identify variables i.e. patient's name, gender, age, ID number, registration date, ultra sound abdomen, ALT, albumin, Prothromb in time, platelet count, previous HCV treatment history, genotype, pretreatment viral load, end of treatment and 12-weeks post treatment viral loads, treatment initiation, completion and SVR dates, hemoglobin (Hb) determination over the course of treatment and treatment outcomes. SPSS analysis software (version 2.2.2.183, Epi Data Association, Odense, Denmark) was used for descriptive statistics describing the study population and treatment outcomes. Relative risks with 95% confidence intervals were calculated as measures of association for factors possibly associated with pretreatment attrition and adverse outcomes

RESULTS

A total of 340 patients were enrolled with 204 male and 136 female subjects. The mean age of patients was 40 years ($\pm$4yrs). Baseline serum ALT was 80 IU/l ($\pm$50.24 IU/l), mean Hemoglobin was 12.9($\pm$2.10g/dl), mean platelet count was161216.32 per mm^3 ($\pm$82835.01) and total leukocyte count as 6224.20 per mm^3 ($\pm$4966.22).All patients were treatment naïve and non-cirrhotic i.e. Child Pugh class <5 and no cirrhosis on ultrasound. The results are shown in table 1.

Table 1. Parameters of the subjects studied

No of Patients (n=340)	Baseline ALT (IU/l)	Mean Hb (mg/dl)	Mean platelet Count (per mm^3)	Mean Leucocytes Count (per mm^3)
Male (n=204)	80	12.9	161216	6224
Female (n=136)				
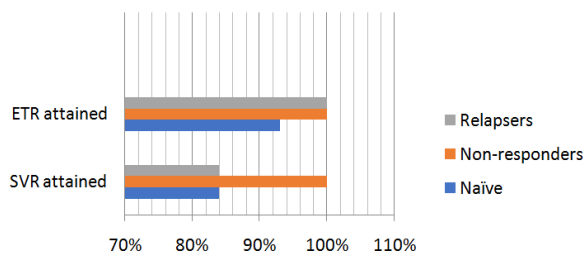
Figure No.1: Details of Patients attaining SVR, ETR and RVR

Amongst 340 patients, 10 patients got dropped out of the study. 2 females due to pregnancy and 7 patients

(male=3 and female=4)lost to follow up. In 1 female, treatment was discontinued due to development of severe anemia (which improved after stopping treatment). 318(96.25%) patients achieved a ETR. SVR 12 was successfully achieved by 306 (92.78%) patients.The results are shown in figure 1.

Adverse effects: All330patients who completed treatment, anemia in 10, fatigue in 8 and headache in 12 subjects were the most common side effects which were managed with paracetamol and counselling (the effects didn't lead to discontinuation of treatment). Moderate anemia (<10g/dl peaked at week 8) was detected in 35.55% (n=117) patients. The dose of Ribavirin was reduced as per recommendation, and patients were monitored for symptomatic anemia along with folate supplementation without discontinuation of treatment. One female patient developed progressive decline in hemoglobin during the 1st month of treatment, as a consequence of which treatment was discontinued.

DISCUSSION

The novel approach of Hepatitis C management using DAAs simple regimens with fixed dose of Sofusbuvir and weight-based Ribavirinyielded a treatment success rate of 94%. These results show how we have successfully simplified HCV management in a high-burden setting, and confirm under real world conditions the high efficacy of DAAs that has previously been reported in the controlled environment of clinical trials.[16-19]

The use of the Sofosbuvir-Ribavirin (SOF-RBV) treatment regimen in the Pakistani context is not new, given that Sofosbuvir was registered in Pakistan since November 2014.[20] Treatment outcomes for this setting are now coming up in different settings and regions of the country. Bannu and its surrounding districts are harbouring one of the highest burden of CHC in this province. In this study, an integrated, standard model of care for HCV was effective, with loss-to-follow-up rates at 10%. The outcomes and treatment characteristics are in line with published evidence from other settings. The new all-oral treatment regimen is highly tolerable with documented limited adverse events in clinical trials. The VALENCE study, a multicenter Phase 3 trial in Europe showed that the SOF-RBV regimen for 24 weeks in GT3 patients had an SVR12 of 85% [18], we had a higher rate of SVR12 attributed to limiting the study only to non cirrhotic treatment naïve patients. Conventional management relying on an IFN-based treatment regimen over a prolonged time period[10] resulted in general SVR rates of 42–93% for all genotypes, showing only moderate efficacy for the combination of pegylated IFN with Ribavirin in multiple randomized control trials.[19] A real life, retrospective study done at Queen's Liver Center in Hawaii, on treatment outcomes as compared to the VALENCE study for GT3 patients on SOF-RBV

regimen for 24 weeks showed SVR rates of 81%. [21] Two Indian studies gave initial real-life results from a treatment cohort of GT3 patients receiving 24-week of SOF-RBV, with SVR12 rates at 96% regardless of severity of disease or previous HCV treatment history.[22,23]

Hemolytic anemia associated with Ribavirin is commonly seen in patients on a SOF-RBV regimen.[18,20] An Hb reduction of 2.1 g/dl for a 24 week SOF-RBV treatment course for GT3 patients was observed in the VALENCE study with 6% of patients having Hb levels less than 11 g/dl at any point in the treatment.[18] Our treatment cohort recorded 35% of patients developing moderate anemia with Hb less than 10g/dl at any time during the treatment course. Despite temporary discontinuation of treatment for one patient with severe anemia, SVR12 was achieved.

The following limitations were identified for this study. First, as the study reflected an interim analysis for only 24 months, only a limited sample size for treatment outcomes could be obtained. This affected analysis in terms of establishing strong associations with adverse outcomes. Secondly patients were only studied till SVR12 and therefore subsequent duraibility of SVR couldn't be evaluated, however we continue following these patientds for the same Third, data regarding patient's previous HCV treatment history may have been inflated, as some patients were not able to present documents evidencing past HCV medical management; however, they were still included as patients with previous HCV treatment. Strengths included the operational nature of the study, ensuring that the results likely reflect the field conditions encountered by many operational actors; and adherence to the STROBE guidelines for reporting of observational data.[21]

Our management of CHC showed good treatment outcomes. It ensured adherence to treatment through monthly follow-ups with patient support component, which likely contributed to the positive outcomes. In underserved areas of the United States the concept of task-shifting was developed, engaging mid-level healthcare practitioners in the management of CHC with DAAs with indirect supervision from a specialist: an SVR12 was achieved for 83% of GT3 patients in this treatment cohort.[22] Another study involving the Extension for Community Health Outcomes (ECHO) Model engaging PHC management of CHC in New Mexico, USA by training primary care providers showed overall SVR12 rates of 58.2%.[23] Overall, the encouraging programmatic outcomes suggest that the decentralized approach can serve as a model for other stakeholders contemplating a HCV programme.

CONCLUSION

Hepatitis C management in a programmed approach using an integrated and strong follow up, using direct-acting antivirals, produces treatment outcomes comparable to clinical trials done for Sofosbuvir-based treatment regimens.

Author's Contribution:

Concept & Design of Study:	Mohammad Omar Khan, Wasim Ahmad
Drafting:	Naseeb Rehman
Data Analysis:	Abdul Razaq
Revisiting Critically:	Abdul Razaq, Wasim Ahmad
Final Approval of version:	Mohammad Omar Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

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