

EFFICACY OF SOFOSBUVIR AND RIBAVIRIN BASED TREATMENT IN CHRONIC HEPATITIS C GENOTYPE 3 PATIENTS

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Abstract

Introduction: Hepatitis C virus (HCV) infection represents a major healthcare challenge in both industrialized and developing countries. The standard treatment for hepatitis C virus (HCV) infection has been interferon-based over many years with less than satisfactory cure rate and many side-effects. Directly acting antivirals (DAAs) have promise for a treatment regimen free of interferons with much better cure rate and minimal side-effects.

Aims and Objectives: To evaluate efficacy and safety of an oral interferon-free regimen, sofosbuvir plus ribavirin in the treatment in genotype 3 chronic hepatitis C patients.

Materials and Methods: 200 treatment naïve chronic hepatitis C genotype 3 patients of either sex with age more than 18 years were enrolled in the study. Sofosbuvir 400 mg once daily plus Ribavirin weight-based was given to all the patients. Duration of treatment was 24 weeks and 12 weeks to cirrhotics and non-cirrhotics respectively.

Data analysis was performed using the IBM SPSS version 22.

Results and Observations: In this prospective study the total number of patients was two hundred (n=200). The mean age (in years) of patients was 44.2 ± 14.7. The number of male patients was 112 (56 %) and 88 (44 %) were females. The number of cirrhotic patients was 70 while 130 were non-cirrhotic.

On comparison on the basis of sustained virological response at twelve weeks of the completion of treatment (SVR12) we observed that treatment naïve cirrhotic patients had SVR 12 of 92.8 % while in the non cirrhotic patients SVR 12= was 96.9 % . Adverse effects were insignificant and none of the patients dropped out because of side effects.

Conclusion: The sofosbuvir and ribavirin based therapy showed very good rates of sustained virological response in chronic hepatitis C genotype 3 patients irrespective of the state of fibrosis. In addition it was found to be cost effective, safe and very well-tolerated.

Keywords: Hepatitis C; Genotype 3; directly acting antivirals, Sofosbuvir, Sustained virologic response (SVR).

Introduction

Viral hepatitis is estimated as the 7th leading cause of global mortality, with about 50% of these deaths caused by HCV and its complications.(1)The goal of HCV therapy is to cure the infection, i.e. to achieve a sustained virologic response (SVR) defined as undetectable HCV RNA 12 weeks or 24 weeks after treatment completion.SVR12 and SVR24 have been accepted as endpoints of therapy by regulators (2). Genotype 3 is the most common genotype in India.(3)

Treatment with pegylated interferon (PEG IFN) and ribavirin (RBV) had been standard care for HCV patients for a more than a decade, until the arrival of oral drugs direct acting antivirals (DAA). The availability of all-oral, direct-acting antiviral (DAA) drug combinations with high efficacy, favourable side-effect profile and easy applicability

facilitated treatment of HCV infection in clinical practice.(4,5).

Sofosbuvir (SOF), a first in-class nucleotide NS5B polymerase inhibitor with a high barrier to resistance, was approved for interferon-free treatment of HCV infection in the USA and Europe in early 2014.(6) Directly acting antivirals (DAAs) have led to high sustained virologic responses (SVRs) than interferon based regimens, are shorter in treatment duration, are orally administered and have fewer adverse effects.

In this study, we report our experience with direct antiviral agents (DAAs) based treatment regimens of chronic hepatitis-C genotype-3 infection in Kashmiri population.

Aims and Objectives

- To evaluate the efficacy of Sofosbuvir plus Ribavirin in chronic hepatitis C genotype 3 patients.

- To assess the safety and tolerability of this drug regimen.

Materials and Methods

This study was conducted in the Departments of Gastroenterology, Government Medical College, Srinagar and Sher i Kashmir institute of medical sciences Soura, Srinagar Kashmir India from May 2015 to April 2017. These are the two largest tertiary care hospitals in the whole state of Jammu and Kashmir which is the northern-most state of India. The study was started after clearance from local institutional ethical committee. Written informed consent requirement was waived because the patients' data were de-identified.

Inclusion criteria: 200 newly diagnosed adult patients of chronic hepatitis C with genotype-3 cirrhotic as well as non-cirrhotics of either gender were included in this study.

Exclusion Criteria:

Co-infection with Hepatitis-B or Hepatitis-D or HIV.

Children, pregnant patients and ESRD/patients on hemodialysis

Evidence of liver disease because of other etiology.

Contraindication to RBV therapy, chronic use of systemically administered immunosuppressive agents and history of solid organ transplantation

Study Design: All the patients selected for this were randomized into two groups:

Group-A (non-cirrhotic) received sofosbuvir (400mg per day) and ribavirin weight-based for a period of 12weeks.

Group-B (Cirrhotic) received sofosbuvir (400mg per day) and ribavirin body weight based for a period of 24 weeks.

Assessment of liver stiffness was done with Fibrosacan (ECHOSENS France) transient elastography which is a reliable and recommended non-invasive tool to detect significant fibrosis or cirrhosis in patients with chronic hepatitis-C. The cut off value of 13 kPa was taken for cirrhosis. Baseline investigations including Hematological and biochemical tests including complete blood count, liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBiL], albumin, and prothrombin time [PT]), renal function tests (creatinine and blood urea nitrogen), ultrasonography, weight, height was taken.

The anti-HCV antibodies were detected by using Enzyme Linked Iso-immuno Assay (ELISA) technique. HCV RNA level was measured by COBAS AmpliPrep/COBAS TaqMan HCV test, v2.0 (Roche Molecular Diagnostics, Branchburg, NJ) with a lower limit of quantitation of 15 IU/mL After determining the HCV-genotype, patients with genotype 3

were included in the study protocol. Esophageal varices were screened by upper gastrointestinal endoscopy (Olympus GIF Q 150 series).

After putting the patients on treatment, HCV-RNA load was measured at 4 weeks, at the end of treatment and 12 weeks post-treatment. Safety was evaluated by monitoring adverse events (AEs), concomitant medication use, vital sign measurements and physical examinations. AEs were recorded from baseline through post-treatment Week 4.

Statistical Analysis: It was a randomized, open label, prospective, hospital based, comparative study. Data analysis was performed using the IBM SPSS version 22. Continuous variables are expressed as mean \pm standard deviation, whereas categorical variables are shown as numbers and percentages. For univariate analysis, a χ^2 test or Student's t-test was used when appropriate. And for multivariate analysis, logistic regression was used. $P < 0.05$ was regarded as statistically significant.

Results

Table 1: Baseline Characteristics of the patients

| Variable | |
|--------------------------------------------------|------------------------|
| Mean age years (SD) | 44.2 \pm 14.7 |
| Male: female % | 56.5 : 43.5 |
| BMI, Mean kg/m ² (SD) | 26 (\pm 5.5) |
| Cirrhosis n (%) | 70 (35%) |
| Bilirubin Total (mg/dl) mean \pm SD | 0.8 (\pm 0.6) |
| ALT(ULN:40U/L) mean \pm SD | 44 (\pm 25) |
| AST(ULN:40 U/L) mean \pm SD | 42 (\pm 23) |
| Albumin (g/dl) mean \pm SD | 3.9 (\pm 0.8) |
| INR mean \pm SD | 1.1 (\pm 0.3) |
| TLC(x1000/mm ³), mean \pm SD | 5.5 (\pm 2.8) |
| Hemoglobin(g/dl), mean \pm SD | 11.8 (\pm 4.2) |
| Platelets(x1000/mm ³), mean \pm SD | 180 (\pm 110) |
| Creatinine (mg/dl), mean \pm SD | 0.9 (\pm 0.3) |
| HCV RNA mean \pm SD IU/ml | 650000 (\pm 150000) |
| MELD score, median (range) | 12 (5-8) |

In this prospective study the total number of patients analysed was two hundred (n=200). The mean age (in years) of patients was 44.2 \pm 14.7.

The number of male patients was 113 (56.50 %) and female patients were 87 (43.50)

Gender of the patient was not found to be a significant factor in achieving SVR in our study.

Table 2: Distribution of among cirrhotics and non-cirrhotics

| | Frequency | Percentage |
|----------------|-----------|------------|
| Non-cirrhotics | 130 | 65 % |
| Cirrhotics | 70 | 35 % |
| | 200 | 100 % |

The number of cirrhotic patients was 70 (35 %) while 130 (65 %) were non-cirrhotic.

In cirrhotic group 65 / 70 i.e approximately 93 % achieved SVR.

Table 3: Among non-cirrhotics 125/130 i.e approximately 97 % achieved SVR.

| SVR 12 ACHIEVED | Non-cirrhotics | | Cirrhotics | |
|--------------------|-------------------|----------------|--------------|-------------|
| | YES N (%) | NO N (%) | YES N (%) | NO N (%) |
| | 125/130 (96.9) | 5/130 (3.1) | 65 (92.8) | 5 (7.2%) |

Table 4: Adverse events (AEs)

| Adverse events | Frequency | Percentage |
|-------------------------------|-----------|------------|
| Fatigue | 24 | 12 |
| Anemia a | 18 | 9 |
| Headache | 16 | 8 |
| Dry Mouth | 16 | 8 |
| Fever | 10 | 5 |
| Dyspepsia | 16 | 8 |
| Decreased appetite | 14 | 7 |
| Insomnia | 12 | 6 |
| Myalgia | 16 | 8 |
| AE leading to discontinuation | 0 | 0 |
| Death | 0 | 0 |

A Anemia was defined as a hemoglobin level <100 g/L or a decrement of >10% from baseline.

Commonly observed adverse effects were fatigue, anemia, headache, dyspepsia dry-mouth. None of the patients had any severe side effect and none dropped out of the treatment protocol..

Discussion

Patients with HCV genotype 3 infections are considered a special population because they are difficult to treat, have faster progression to cirrhosis, lowest SVRs even in the DAA era.

In Kashmir, a northern state of India, DAAs like Sofosbuvir (NS5B inhibitor) became available by the end of 2014 which opened ways for a possible all-oral, interferon-free regimens.

In this study, we report our experience with direct –acting antiviral agents (DAAs) based treatment regimens of chronic hepatitis-C genotype-3 infection in Kashmiri population.

We enrolled 200 treatment naive chronic hepatitis C genotype 3 patients, both cirrhotic and non-cirrhotic. They were treated with sofosbuvir 400 mg daily and weight – based ribavirin combination, to assess the efficacy safety and tolerability of this treatment regimen.

All of the patients enrolled in this study were asymptomatic, found incidentally or on screening or with some trivial liver enzyme elevations.

In our study most of the patients had no family history of acute or chronic hepatitis C infection. Majority, 80% of patients had no underlying comorbidity. Among the patients studied diabetes mellitus (4.4%), hypertension (3%), leukemia (2%) and carcinoma ovary (1.1%) were the comorbid illnesses.

Patient age has been an important factor to predict SVR in Hepatitis C patients who received PEG-interferon plus Ribavirin treatment. We did not find any significant variation in SVR across various age groups 7, 8

Viral load also remained a significant factor for the determination of SVR in patients who received Interferon-based therapy. No significant relationship between viral load and treatment response was observed in our study. 7, 8

In Valence study [9] among female patients (n=95) SVR12 was 93.7%) and among the male patients (n=155) SVR 12 was 80.0%). We did not see any difference of significance in SVR rates in males and females.

In our study 35 % patients were cirrhotic 70/200 while 65 % were non-cirrhotic.

In cirrhotic group 65 / 70 i.e approximately 93 % achieved SVR.

Among non-cirrhotics 125/130 i.e approximately 97 % achieved SVR.

A similar study by Raese N K et (10) al from India reported SVR 12 of 100 % in treatment naïve hepatitis C cirrhosis treated with Sofosbuvir plus Ribavirin for 24 weeks although total number of patients included was twenty-nine (29) only.

In Valence study [9] among the treatment naïve patients with cirrhosis (n=13) SVR12 of 92% was achieved.

In ASTRAL-3[11] study genotype 3 treatment naïve cirrhotics n=45, when treated with sofosbuvir and ribavirin for twenty four weeks achieved SVR12 of 73%.

In BOSON study[12] among treatment naïve patients (n=94) who received sofosbuvir and ribavirin for twenty four weeks sustained virological response was achieved by 58%, while as in treatment experienced patients (n=88) sustained virological response was achieved by seventy patients (SVR12=80%).

In POSITRON study [13] sofosbuvir and ribavirin as given for only twelve weeks in genotype 3 patients . The high sustained virological response in our study as compared to the POSITRON study can be explained by the fact that extending the treatment duration from twelve weeks to twenty four weeks significantly increases the sustained virological response.

The observation of improved sustained virological response on increasing the treatment duration from twelve and sixteen weeks to twenty four weeks is in agreement with the published data.

In a multicentre study in India (14) Genotype C patients treated with sofosbuvir plus ribavirin combination for 24 weeks showed SVR 12 of 93%.

We reported fatigue as the most common adverse effect. Anemia was seen in 9% patients. None of the patients dropped out of treatment protocol because of adverse effects.

In a study from Germany (15), treatment discontinuation due to AEs was infrequent (2.5%) and most (8/10) occurred in patients with advanced liver disease. Serious AEs were reported in <5% of the patients. Anaemia was frequent in this real-world population (21.2%) and mostly managed with RBV dose reductions.

In the safety analysis of the POSITRON study, fatigue and insomnia occurred at a higher rate in the sofosbuvir-plus-ribavirin-treated patients compared with the placebo-treated patients (fatigue, 44% vs 24%; insomnia, 19% vs 4%). Anemia also occurred more frequently in patients receiving sofosbuvir plus ribavirin. In the FUSION study, the incidence of adverse events did not differ significantly between the 12-week and 16-week groups. In both studies, the overall rate of sofosbuvirplus- ribavirin treatment discontinuation was low (1%-2%). For both studies, the overall toxicity profile was not significantly affected by the presence or absence of cirrhosis at baseline.

Yoon J H et al from Korea (16) reported anemia as the most common adverse event (17.5%), with fatigue being the second most common (11.3%).

Conclusion

Sofosbuvir plus Ribavirin all-oral combination results in high rates of sustained virological response in patients with chronic hepatitis C genotype 3 patients. The cure rate was very high in both cirrhotics and non-cirrhotics. In addition it was safe and well tolerated .

Additional information and declarations

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