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# A Study on the Efficacy of 24 Weeks of Sofosbuvir, Daclatasvir with Ribaravin in the Treatment of Chronic Hepatitis C Patients with Cirrhosis, Genotype 1 and 3.

**Nitali Arun[1], Anand Dev[2], V.K.Singh[3]**

[1]Assistant Professor, Department of Microbiology, TMMC &RC, [2]Assistant Professor, Department of Internal Medicine, TMMC & RC, Moradabad [3]Professor and Head, Department of Internal Medicine, TMMC & RC, Moradabad.

## Abstract

**Background:** A number of new interferon free regimens involving direct-acting antiviral agents have recently been approved in EASL 2016 guidelines for the treatment of chronic hepatitis c, cirrhotic patients with genotype1 and 3. Our aim was to assess the efficacy of one such combination of Sofosbuvir, Daclatasvir with Ribaravin after a period of 24 weeks of treatment. **Subjects and Methods:** 200 patients with hepatitis C and cirrhosis infected with genotype 3 and 1 were included in our study. They were treated with Sofosbuvir 400mg, Daclatasvir 60 mg and weight based Ribavirin for 24 weeks. Response to treatment was assessed 12 weeks after the end of treatment with a sensitive assay (SVR12). **Results:** Sustained virological response after 12 weeks of end of treatment (SVR12) was achieved in 97.8% of the patients. Among the 4 patients who did not achieve SVR, all were infected with genotype 3 suggesting comparatively greater difficulty in treating this genotype with the available DAA's. Treatment had to be discontinued in 3 patients due to rise in serum creatinine following acute gastroenteritis. 2 patients died due to sepsis. The most common treatment related adverse events were fatigue, headache, cough and sleep related disturbances. No treatment related adverse events related in discontinuation of treatment. **Conclusion:** Combination of Sofosbuvir and Daclatasvir with weight based Ribavirin for 24 weeks is highly effective and safe in treating cirrhotic HCV patients with Genotypes 3 and 1.

**Keywords:** Sofosbuvir, Daclatasvir, Ribavarin, Hepatitis C.

**Corresponding Author:** Dr. Anand Dev, Assistant Professor, Department of Internal Medicine, TMMC & RC, Moradabad.

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## Introduction

Hepatitis C infection remains a global health problem and a significant challenge affecting 200 million chronically infected patients worldwide.[1] The estimated prevalence of HCV infection in India is about 1–1.9% although variations have been reported in studies across various regions in India.[2] HCV is a single-stranded RNA virus belonging to the family Flaviviridae. HCV has six major genotypes, with genotype 1 being the most prevalent genotype globally (46%), followed by genotype 3 in 22%.[3-8]

In published studies, genotype 3 has been reported as the most common genotype in India, responsible for 54–80% of case.[9,10]

Epidemiological studies from various regions of India have uniformly shown predominance of genotype 3; however, in southern India, both genotypes 1 and 3 have been reported to be prevalent.[11]

A record number of cases of chronic hepatitis C have been reported from Moradabad and adjoining areas since 2016 when screening programs for the same was started. A total of 313 cases have been officially reported in Teerthanker Mahaveer University since May 2016.Various screening programs outside this university have reported a record total of around 2000 cases in and around Moradabad city since 2016 with genotype 3 being the most common followed by genotype 1.

After the Interferon era the arrival of generic Direct Acting Antivirals (DAA's) like Sofosbuvir in March 2015 and Daclatasvir in December the same year, has unleashed an era of revolution in the management of Hepatitis C especially in resource poor regions like western U.P and Moradabad owing to their higher SVR rates and affordable cost.

Various combinations of DAAs have been proposed in EASL 2016 guidelines for effective treatment of genotype 1 and 3 with cirrhosis. So we decided to evaluate the effectiveness of one such combination of Daclatasvir plus Sofosbuvir with Ribavirin. This evaluation at this point of time in the journey of DAAs could be helpful in making treatment decisions in Chronic Hepatitis C. So, our aim was to assess the efficacy of 24 weeks of Sofosbuvir, Daclatasvir with ribavirin in the treatment of chronic hepatitis C patients with cirrhosis, genotype 1 and 3 in a large diverse population.

## Subjects and Methods

**Study design**

This is a controlled trial that reports the result of treating 200 cirrhotic patients of chronic hepatitis C with Sofosbuvir 400mg and Daclatasvir 60mg along with weight based Ribavirin in the Moradabad district of Uttar Pradesh.

In our study 200 patients with chronic hepatitis C who fulfilled our inclusion and exclusion criteria were selected from OPD and indoor wards of Teerthanker Mahaveer Medical College And University between October 2016 to June 2018.Only genotypes 3 and 1, the genotypes common in and around Moradabad (and western U.P. probably) were included. Treatment decisions were given according to EASL 2016 guidelines. Accordingly patients were given 400 mg of Sofosbuvir and 60 mg of Daclatasvir along with ribavirin 1000-1200mg for a period of 24 weeks.

**Patients**

**Inclusion criteria**

1. Detectable serum HCV RNA
2. Patients with genotype 1 and 3
3. Patients with cirrhosis.
4. Both treatment naïve and experienced.

The gold standard for the diagnosis of cirrhosis is liver biopsy. However it is not done routinely these days. So the diagnosis of cirrhosis in our study was done by Fibroscan (liver stiffness greater than 16.2 Kpa).In cases where fibroscan was not reliable (e.g. due to ascites), cirrhosis was diagnosed based on clinical characteristics such as ascites, splenomegaly, small echogenic liver, esophageal varices, etc.

**Exclusion Criteria**

1. Patients with significant renal failure defined as e GFR < 30.
2. Very advanced disease defined as MELD score > 20 or Child –Pugh score > 12.
3. Chronic liver disease due to other causes.
4. Co-infection with hepatitis B or HIV.
5. Previous treatment failure with Sofosbuvir based regimen.
6. Taking amiodarone within the last 6 months.

**Efficacy Assesment and end Point of Treatment**

Treatment was started with Sofosbuvir 400mg (MY HEP 400) and DACLATASVIR 60mg (MY DECLA 60mg, Mylan Pharmaceuticals) and 1000mg of Ribavarin. Ribavirin was given in two daily divided doses. The treatment duration was 24 weeks for all patients. Patients were called for follow-up every 4 weekly and 12 weeks after the end of treatment. During each visit, a complete clinical examination was done and enquired regarding side effects and compliance. HBV DNA load quantitative was done at baseline, at 4 weeks, at the end of the treatment (24th week) and 12 weeks after the end of the treatment.

Primary efficacy endpoint was SVR12 defined as HCV RNA below the lower limit of quantification or (LLOQ) OR undetectable at least 12 weeks after treatment discontinuation. Per- protocol method was used in determining treatment outcomes and efficacy analysis.

**Safety assessments**

Safety evaluation was done by collecting data during treatment and up to the end of follow-up period (12 weeks after the last dose) by clinical and laboratory examination and documentation of adverse effects.

**Statistical analysis**

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 24.0 for windows. P value <0.05 was considered statistically significant.

## Results

**Table 1: Base Line Characteristics Of The Patients.**

| Variables | Value |
|---|---|
| Number | 200 |
| Sex, M/F | 130/70 |
| Mean age, years | 53.9 |
| **Genotype** | |
| 1a | 70 |
| 1b | 18 |
| 3a | 112 |
| Mean liver stiffness, Kpa | 33.5 |
| Mean viral count, IU/ml | 42,10000 |
| Decompensated cirrhosis | 9 |

**Table 2: Treatment Outcome of The 200 Enrolled Patients With Cirrhosis.**

| Variables | Value |
|---|---|
| Total no. of patients | 200 |
| Treatment discontinued | 3 |
| DIED | 2 |
| Follow-up lost | 9 |
| Completed trial | 186 |
| SVR12 | 182 |
| Genotype 3 | 103/105 |
| Genotype 1 | 79/81 |
| Per- protocol SVR | 97.8% |
| Intention to treat SVR | 91% |

Two hundred patients were enrolled in the present study. The base line characteristics of the patients have been shown in [Table 1].

Three patients with decompensated cirrhosis had gastroenteritis following which serum creatinine levels increased. Treatment had to be discontinued in them as increased creatinine is a contraindication for both Sofosbuvir and Daclatasvir. Subsequently they had to be excluded from our study. Viral load was undetectable in those patients at the 4th week.

We lost two of our decompensated patients due to sepsis and probable DIC. Viral load was undetectable in all of them.

Nine of our patients could not be followed up. Among them eight had finished our prescribed therapy. One hundred and eighty six patients finished the trial and one hundred eighty two among them achieved sustained virological response (SVR12). Viral load was undetectable in all of them when done at the designated 4 weekly interval including the patients who did not turn-up for follow-up. Treatment outcomes have been shown in [Table 2].

The most common adverse effects reported by our patients were fatigue, headache, cough and sleep related disturbances. No significant anemia (>10% decrease in Hb) developed in our patients. No treatment related adverse effects resulted in discontinuation of the treatment. All patients took the full prescribed course of treatment.

## Discussion

This trial showed that treatment with SOF and DCV with ribavirin for 24 weeks is highly effective for patients of both genotypes 1 and 3 with cirrhosis.

Various combinations of Direct Acting Antivirals (DAA's) have been suggested in EASL 2016 guidelines to treat genotype 1 and 3.In the present study we demonstrated the efficacy of this combination in treating patients of Chronic hepatitis C with cirrhosis and genotype 3 (which are considered most difficult to treat) and 1.

We noted an excellent efficacy with SVR of 97.8% in the patients who carried on with our treatment till the end point. Even the Intention-to-treat SVR was 91% which is very good considering cirrhosis and genotype3 which is considered difficult to treat.

In a study by Poordad F, Schiff Eugene R et al,[12] in patients with cirrhosis SVR 12 rate was 82% for genotype 1 and 83% for genotype 2.

In another study by Merat S, Sharifi AH, et al,[13] an SVR12 of 98% was achieved in patients of genotype 1 and 3 in a cohort of Iranian population. In a similar study by Nelson DR, Cooper JN, et al,[14] an SVR 12 of 96% was found in genotype 3 patients without cirrhosis.

With the advent of direct acting antivirals (DΑΑ's) it was being speculated that the role of Ribavirin would be eliminated from the treatment landscape of hepatitis C. But what we observed from our study that Ribavirin certainly can retain its role with authority in the treatment of difficult to treat Hepatitis C patients like genotype 3 and cirrhotic. Addition of Ribavirin to every patient in our study might have a role in maximizing the SVR rates. Some trials have also demonstrated that that it may also be helpful in shortening treatment duration with DAA's. In our trial the severity and frequency of anemia was also not significant as were the other side effects.

We had a total of nine patients with decompensated cirrhosis at the time of enrollment. Among them three patients had to be discontinued from treatment because of rise in serum creatinine levels. Although the remaining six patients with decompensation eventually attained SVR they had to be referred for liver transplantation considering their overall clinical status .Based on our experience we recommend for early liver transplantation in such patients .Whether achieving SVR shall be helpful in delisting such patients from liver transplant remains an area of further research and study.

It is a common practice to continue doing viral counts every 4 weeks even after seeing for early virological response at week 4.In our study we found that viral counts were negative during all the designated weeks in those patients who gave consent for the same. So we suggest that in resource poor regions like western U.P. and Moradabad testing viral counts during treatment may not be necessary although it may be helpful in checking the compliance of the patients. Also negative viral counts might encourage patients to continue treatment.

As has been mentioned in EASL 2016 guidelines that in patients with advanced fibrosis and cirrhosis, an SVR reduces the rate of decompensation and will also reduce, but not abolish, the risk of HCC. Based on this we recommend that even if we achieve an SVR of more than 90% with the combination of DAA's used in our study, surveillance for HCC must be continued every 6 monthly.[15]

Considering the result of this study we believe that Sofosbuvir with Daclatasvir and Ribavirin could be the first choice in treating all cirrhotic hepatitis C patients. Also it might not be even necessary to check genotypes in future and this combination can be used as a "Pan genotypic" regimen.

## Conclusion

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