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Research Article

# Direct Acting Antivirals in Hepatitis C Virus Genotype 3 and Advanced Cirrhosis

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## 1. Abstract

**1.1. Aim:** Direct-Acting Antivirals (DAAs) have revolutionized the management of hepatitis C infection. However, genotype 3 cirrhosis is still difficult to treat. We report our experience in the management of genotype 3 cirrhosis with DAA's.

**1.2. Methods:** We analysed 111 adult cirrhotics with genotype 3 infection of which 54 (48.6%) had Decompensated Cirrhosis (DC). Patients with Compensated Cirrhosis (CC) received sofosbuvir (SOF), pegylatedinterferon (PEG-IFN) and ribavirin (RBV) for 12 weeks (group1; n=13) or SOF, daclatasvir (DCV) and RBV for 24 weeks (group2; n=44). DC patients received SOF, DCV, and RBV for 12 or 24 weeks (group 3; n=37). Untreated DC patients acted as controls (group 4; n=17). The primary endpoint was sustained virological response at 12 weeks (SVR12).

**1.3. Results:** SVR12 was achieved in 96.4% of CC and 94.5% of DC patients. SVR12 was higher in group 2 as compared with group1in CC (100% vs. 84.6%, p=0.049). SVR12 was comparable in DC treated with SOF, DCV and RBV for either 12 or 24 weeks (92.3% and 95.8%; p=1.0). Side effects were more common in group1 compared to group 2 (100% vs. 22.7%; p<0.001). Side effects were noted in 40.5% patients in group 3, predominantly fatigue and anemia.

**1.4. Conclusions:** DAA's are safe and effective in treatment of genotype 3 cirrhosis. SOF, DCV and RBV combination is superior to SOF, PEG-IFN, and RBV in CC. Treatment with SOF, DCV, and RBV for 12 or 24 weeks were comparable in DC.

**2. Keywords**: Chronic hepatitis c; Genotype 3; Direct acting antivirals; Decompensated cirrhosis

## 3. Introduction

Prevalence of Hepatitis C Virus (HCV) is estimated to be around 0.5-1% in our country [1]. Data published from various parts of country suggests that Genotype 3 contributes to around 55-80% among all genotypes [2, 3]. Different genotypes of HCV have more than 34% genetic variability, making it a difficult to treat virus and also mutations on treatment are hinderance to successful eradication. Introduction of interferons although opened a way to treating this innocuous virus, however, intramuscular injections, cytopenias, fever, malaise and poor patient compliance were important reasons for treatment discontinuation or non-preference. Subsequently, with availability of Direct Acting Antivirals (DAAs), the treatment of Chronic Hepatitis C (CHC) became simple, of short duration, easy to administer and monitor. Rapidly, DAAs replaced the interferons for CHC. Genotype 3 had a better response with interferons as compared to genotype 1.On the contrary; DAAs had a better response towards genotype 1 than genotype 3. ALLY-3 trial showed that sofosbuvir (SOF) and daclatasvir (DCV) for 12 weeks had sustained virological response (SVR) rate of 97% in treatment naïve non-cirrhotic CHC patients, however, SVR rate declined to 58% in treatment naïve compensated cirrhosis patients [4]. Subsequently, addition of ribavirin (RBV) to SOF and DCV for 12/16 weeks in ALLY-3+ study showed SVR rate to improve to 86% in treatment naïve compensated cirrhosis genotype 3 CHC patients [5]. Therefore, we aimed to study the efficacy and safety of DAAs in HCV genotype 3 patients with advanced cirrhosis.

## 4. Methods

This was a retrospective analysis of patients with HCV cirrhosis attending a tertiary centre from December, 2014 to January, 2017. All patients aged more than 18 years diagnosed with HCV genotype 3 infections with evidence of cirrhosis were included in the study. Cirrhosis was diagnosed based on Transient Elastography [6-8] with Liver Stiffness Measurement (LSM) >12.5 kPa or ultrasonography i.e. presence of shrunken and nodular liver, widened interlobar fissure, portal vein diameter >14 mm, splenomegaly, and presence of ascites or liver biopsy if needed. Patients with Decompensated Cirrhosis (DC) presented with either jaundice or ascites or upper gastrointestinal bleed or Hepatic Encephalopathy (HE). Patients with age <18 years, hepatocellular carcinoma, presence of co-morbid conditions like chronic renal disease, cardiac disease, psychiatric illnesses and anemia were excluded from the study. All patients were diagnosed with anti-Hepatitis C antibody by Enzyme liked immunoassay (ELISA). Subsequently, all patients with positive test for antibody underwent HCV RNA quantitative levels by quantitative real time polymerase chain reaction using Cobas Taqman 48 with a lower limit of detection <15IU/mL at baseline. HCV geno type was performed by real time PCR assay. Patients were divided into four groups: Group 1 and 2 were Compensated Cirrhosis (CC) and group 3 and 4 were DC. Group 1 (CC) received pegylated interferon (PEG-IFN), SOF and RBV for 12 weeks, group 2 (CC) received SOF, DCV and RBV for 24 weeks, group 3 (DC) received SOF, DCV and RBV for 12 (3A) and 24 (3B) weeks. Group 4 (DC) included patients who were untreated before the availability of DAAs. RBV was prescribed as per patient tolerability and dose was adjusted with close monitoring for anemia. Sustained virological response (SVR12) was defined as undetectable HCV RNA at 12 weeks after treatment completion.Primary endpoint was taken as SVR at 12 weeks and secondary end points were taken as improvement in clinical scores like Child-Turcotte Pugh (CTP), Model for End Stage Disease(MELD) and control of ascites.

## 5. Statistical Analysis

A descriptive analysis was done for all clinical parameters at baseline. Quantitative variables were presented as mean with range and/ or standard deviation and qualitative variables as proportions with percentages. Comparison between groups was done using student's *t*-test and Mann-Whitney test for parametric and non-parametric variables, respectively, and $\chi^2$ and Fisher exact test were used for categorical variables. A P value ≤0.05 was considered significant. Statistical analysis was performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL).

## 6. Results

A total of 111 patients with HCV genotype 3 cirrhosis were included in the study. The mean age was48.68±9.1 years with male predominancen=77 (69.4%).Out of all patients, 57 (51%) were CC and 54(48.6%) were DC. There were 13, 44, 37 and 17 patients in group 1, 2 3 and 4, respectively. Group 3 had 13 and 24 patients in group 3A and 3B, respectively. HBV-HCV co-infection was present in 4 patients with 2 each in group 2 and 3B. HIV-HCV co-infection was present in 6 patients with 2 each in group 2, 3B and 4. Fifteen patients were treatment experienced with 4 each in group 1 and 2; 3 each in group 3B and 4 and there was 1 patient in group 3A. The baseline mean CTP score in group 1 and 2 combined, group 3 and group 4 was 5.4±0.6, 7.9±1.5, 7.8±1.4, respectively. The mean baseline MELD score in group 1 and 2 combined, group 3 and group 4 was 10±2.6, 12.8±4.2 and 12.8±3.9, respectively (Table 1).

Ascites was present in 35/ 37 in group 3 and 16/17 patients in group 4 with DC at baseline. Out of these, spontaneous bacterial peritonitis was seen in 11 and 7 patients in group 3 and 4, respectively (Table 1). Jaundice was present in 6 patients each in group 3 and 4 and upper gastrointestinal bleed in 10 and 9 patients in group 3 and 4, respectively. Four and 5 patients in group 3 and 4had history of previous HE, respectively. In group 3B, 3 patients had Hepatocellular Carcinoma (HCC).

**Table 1:** Baseline characteristics of CHC patients (n=111)

| Variables | | Group I (n=13)] | Group 2 (n=44)] | Group 3A (n=13)] | Group 3B (n=24)] | Group 4 (n=17) |
|---|---|---|---|---|---|---|
| Demographics | Age | 52±7.4 | 43.7±11 | 52±7.4 | 43.7± 11 | 44.4± 6.5 |
| | Males | 6 | 33 | 6 | 19 | 13 |
| Associated Factors | Alcohol | 1 | 10 | 3 | 8 | 5 |
| | HIV | 0 | 2 | 0 | 2 | 2 |
| | HBV | 0 | 2 | 0 | 2 | 0 |
| Laboratory values | Hemoglobin (gm/ dL) | 12.1±2.4 | 13.3±3.0 | 9.8±1.80 | 10.72±2.04 | 9.8±2.39 |
| | TLC ($10^3$/$mm^3$) | 5.8 ±2.2 | 7.2±2.9 | 4.8±1.2 | 6.1±2.6 | 5±2.2 |
| | Platelets* ($10^9$/L) | 124 | 157 | 101 | 98 | 92 |
| | | (45-344) | (53-325) | (54-149) | (57-147) | (49-209) |
| | Total Bilirubin (mg/dL) | 1.34±0.8 | 1.21±0.5 | 1.10±0.5 | 1.85±1.5 | 1.88±1.3 |
| | Albumin, (gm/dL) | 3.6± 0.6 | 3.8± 0.5 | 3.21±0.6 | 2.92±0.5 | 3.29±0.6 |
| | Creatinine (mg/dL) | 0.76±0.2 | 0.8±0.2 | 1.04±0.5 | 1.06±0.6 | 0.99±0.3 |
| | INR | 1.2±0.1 | 1.12±0.1 | 1.38±0.2 | 1.41±0.2 | 1.44±0.2 |
| Scores | CTP* | 5(5-6) | 5(5-6) | 8(6-12) | 8(6-12) | 8(6-11) |
| | MELD* | 10(6-14) | 10(6-14) | 11(7-22) | 12(7-24) | 12(6-21) |
| Treatment History | Treatment Experienced | 4 | 4 | 1 | 3 | 3 |
| Decompensation | Ascites | - | - | 12 | 23 | 16 |
| | Jaundice | - | - | 4 | 2 | 6 |
| | Bleed | - | - | 2 | 8 | 9 |
| | Encephalopathy | - | - | 3 | 1 | 5 |
| | SBP | - | - | 4 | 7 | 7 |
| Co-morbid conditions | DM | 4 | 4 | 2 | 1 | 2 |
| | HTN | 5 | 5 | 4 | 1 | 4 |
| | HCC | 0 | 0 | 0 | 3 | 0 |

All values are presented as Mean± SD except those indicated by asterisk *. HIV, human immunodeficiency virus; HBV, hepatitis B virus; TLC, total leukocyte count; INR, international normalized ratio; CTP, Child-Turcotte Pugh score; MELD, Model for end stage liver disease; SBP, spontaneous bacterial peritonitis; DM, diabetes mellitus; HTN, hypertension; HCC, hepatocellular carcinoma

### 6.1. Primary endpoint

Group 1 with CC (n=13) received SOF, PEG-IFN and RBV for 12 weeks, group 2 (n=44) with CC received SOF, DCV and RBV for 24 weeks, group 3 (n=37) with DC received SOF, DCV and RBV for 12 (3A,n=13) or 24 (3B, n=24) weeks and group 4 (n=17) was

untreated DC before the availability of DAAs. The SVR rate of group 1 was 11/13 (84.6%), group 2 was 44/44 (100%), group 3A was 12/13 (92.3%), group 3B was 23/24 (95.8%) and group 4 was 0/17 (0%) (Figure 1).

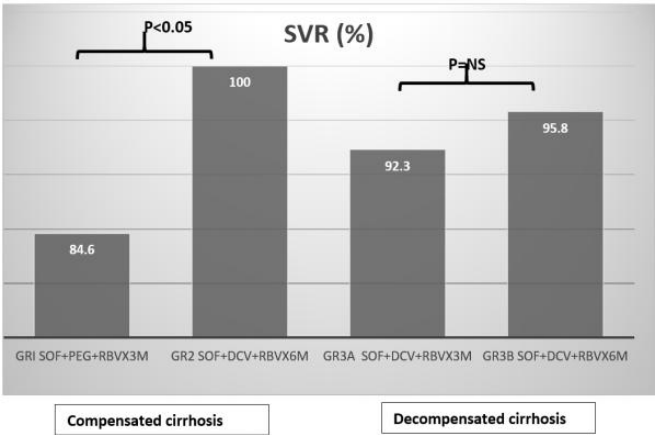


**Figure 1:** Sustained Virological Response (SVR) rates in different groups of CHC patients receiving treatment.

### 6.2. Secondary endpoints

**6.2.1. Improvement in CTP and MELD scores:** In CC (both group 1 and 2), there was a significant improvement in CTP score (5.4±0.6 to 5.1±0.4; p=0.005) and MELD scores (10.0±2.1 to 8.9±2.6; p=0.034) (Figure 2). In group 3 (DC), mean CTP improved (7.9±1.5 to 6.7±1.3; p=0.001) and MELD score had a trend towards improvement (12.8±4.2 to 11.05±4.2; p=0.082) whereas there was no change in CTP (7.8±1.4 to 8.29±1.7; p=0.456) and MELD (12.8±3.9 to 13.7±3.9; p=0.522) in group 4 (DC untreated). In group 3 there was significant improvement in INR values from 1.40±0.24 to 1.26±0.23 (p=0.013). the bilirubin and creatinine values improved in group 3 after treatment, however it was not statistically significant (Table 2).

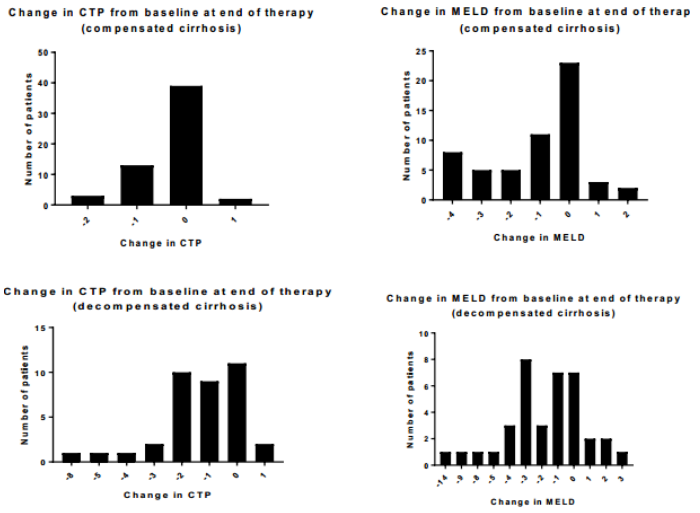


**Figure 2:** Change in CTP and MELD after treatment in compensated (2A,2B) and decompensated cirrhosis (2C,2D).

**6.2.2. Improvement in Ascites:** In group 3, 32 out of 35 patients (91%) showed significantly better control of ascites (p<0.01), whereas only 4 out of 16 patients (25%) in group 4 had better control of ascites (p=NS). There was trend towards improvement in serum albumin values from 3.02±0.61 to 3.21±0.58 (p=0.186) in group 3 (Table 2).

In group 3, after DAA treatment, one patient had episode of HE, one had upper gastrointestinal bleed and one had SBP. Out of 6 patients, 4 patients had improvement in jaundice after treatment in group 3.

**Table 2**: Comparison of different clinical parameters in different groups at baseline and after treatment

| | | Group 3 (n=37) | | | Group 4 (n=17) | | |
|---|---|---|---|---|---|---|---|
| Variables | | Before Treatment | After Treatment | P Value | Before Treatment | After Treatment | P Value |
| Laboratory values | Hb (gm/dL) | 10.42±1.99 | 10.34±1.91 | 0.855 | 9.8±2.39 | 9.85±1.89 | 0.99 |
| | Platelets ($10^9$/L)* | 96 (7.3-333) | 88 (28-213) | 0.9 | 92 (49-209) | 96 (31-192) | 0.702 |
| | Bilirubin (mg/dL) | 1.58±1.32 | 1.69±1.38 | 0.73 | 1.88±1.37 | 1.54±1.08 | 0.176 |
| | Albumin, (gm/dL) | 3.02±0.61 | 3.21±0.58 | 0.186 | 3.19±0.60 | 3.11±0.67 | 0.362 |
| | Creatinine (mg/dL) | 1.05±0.58 | 1.07±0.65 | 0.889 | 0.99±0.34 | 1.07±0.45 | 0.201 |
| Scores | INR | 1.40±0.24 | 1.26±0.23 | 0.013 | 1.44±0.27 | 1.49±0.22 | 0.477 |
| | CTP* | 8(6-12) | 6.5(5-11) | 0.001 | 8(6-11) | 8(6-12) | 0.168 |
| | MELD* | 12(7-24) | 10(6-20) | 0.082 | 12(6-21) | 14(8-20) | 0.34 |
| Clinical parameters | Ascites | 35 | 13 | <0.001 | 16 | 16 | NS |
| | Jaundice | 6 | 2 | 0.261 | 6 | 6 | NS |
| | Bleed | 10 | 1 | 0.006 | 9 | 9 | NS |
| | Encephalopathy | 4 | 1 | 0.357 | 5 | 5 | NS |
| | SBP | 11 | 1 | 0.003 | 7 | 7 | NS |

All values are presented as Mean± SD except those indicated by asterisk *. INR, international normalized ratio; CTP, Child-Turcotte Pugh score; MELD, Model for end stage liver disease; SBP, spontaneous bacterial peritonitis

**6.2.3. Adverse events:** In group 1, 13 /13 (100%) patients had flu-like illness, fatigue and cytopenia; in group 2, 10/44 (22%) patients had fatigue and gastrointestinal intolerance and in group 3 and 4 combined had fatigue in 15/54 (40%) and anemia in 8/54 (22%) patients (Table3).

**Table 3**: Adverse events in different groups of CHC patients receiving treatment

| Treatment Regimen | Adverse events | N (%) |
|---|---|---|
| **Group 1** | Flu-like illness, fatigue and cytopenia | 13(100) |
| **Group 2** | Fatigue and Gastrointestinal intolerance | 10(22.7) |
| **Group 3 and 4** | Fatigue | 15(40.5) |
| | Anemia | 8(21.6) |

## 7. Discussion

The present study evaluated the efficacy of DAAs in HCV genotype 3 including both compensated and decompensated cirrhosis. In CC GT3, efficacy of combination of SOF, DCV and RBV for 24 weeks was 100%. On the other hand, in decompensated cirrhosis GT3, combination therapy of SOF, DCV and RBV had equal efficacy irrespective of 12/24 weeks of duration.

In CC group there was significant improvement in CTP and MELD scores after treatment. In DC patients, there was significant improvement in CTP score and there was trend towards improvement in

MELD score. Decompensated cirrhosis patients who were untreated before the availability of DAAs was included as group 4. These patients showed worsening of CTP and MELD scores without any antiviral treatment. In HCV GT3 DC patients receiving DAAs, ascites improved in significantly higher number of patients than in patients without any treatment [9] in French early access program, found no significant difference in SVR rate 82% vs 86% (45/55 vs 129/150) in HCV GT3 CC patients receiving SOF+DCV for 24 wks irrespective of use of RBV [10] in HCV GT3 CC patients found SVR rate of 83% (5/6) on SOF+DCV+RBV for 12 wks, however the number of patients was very small [11]. In an Italian study found SVR rate of close to100 % (85/85 vs 20/21) in HCV GT3 CC patients receiving SOF+DCV with or without RBV. We found SVR rate of 100% in HCV GT3 CC patients on combination therapy of SOF+DCV+RBV for 24 weeks which is comparable and better than all previous studies. Ribavirin addition in these patients reduces the chances of mutagenesis in hepatitis C virus and improves the SVR rates especially in difficult to treat CHC GT3 CC patients.

In UK expanded access program, [12] showed 71% (75/105) SVR rate of 12 weeks treatment of SOF, DCV and RBV in HCV GT3 decompensated cirrhosis which was better than SOF and DCV (60%; 3/5) for 12 weeks, although the number of patients in group without ribavirin was small. In ASTRAL-4 study [13], combination of SOF and velpatasvir (VPV) for 12/24 weeks in HCV GT3 cirrhosis patients had SVR rate of only 50% and addition of RBV improved SVR rate to 85%. Latest combination of glecaprevir and pibrentasvir has shown SVR rate of 98% (39/40) in HCV GT3 cirrhosis patients, however CTP score was 5/6 in most of the patients [14]. The better SVR rate in our study may be due to difference in virus genetics and mutation in western and our part of the world.

In our country we have highest prevalence of HCV GT3 which even in the era of DAAs has appeared to be difficult to treat genotype, particularly in cirrhosis of liver. We have documented that in GT3 cirrhosis patients 24 weeks of SOF, DCV and RBV had 100% SVR rate. Even in GT3 decompensated cirrhosis, combination of SOF, DCV and RBV had SVR rate up to 94-100% irrespective of treatment duration of 12/24 weeks. Our study has clearly shown that there is improvement in all parameters as well as new events of ascites, HE, upper gastrointestinal bleed and SBP are reduced significantly after successful treatment. Therefore, all decompensated cirrhosis HCV GT3 patients should be treated at earliest and adequately with close monitoring for a better outcome.

## 8. Acknowledgements

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