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Original Research Article

Pan genotypic response to combination treatment with Sofosbuvir and Daclatasvir in chronic Hepatitis C patients

Anup Sreedharan Nair, Thazhath Mavali Ramachandran* and Geevarghese Prajob Prasad

Department of Gastroenterology, Govt. Medical College, Calicut, Kerala, India

QR Code

***Correspondence Info:**
Dr. Thazhath Mavali Ramachandran
Additional Professor,
Department of Gastroenterology,
Govt. Medical College, Calicut, Kerala, India

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Abstract

Background and aims: Hepatitis C is a major cause of liver related morbidity and mortality. Prevalence of HCV infection in India has been variously estimated as 0.9 to 1.9%. With the advent of DAAs, the treatment has been revolutionized with more than 95% cure rate as observed in Caucasian population, while only scarce data on the same are available in the Indian population. Our study is aimed to assess the pan genotypic treatment response (SVR 12) to Sofosbuvir and Daclatasvir combination.

Methods: Chronic hepatitis C patients who attended the department of gastroenterology in Calicut Medical College, Kerala, India were included in the study. All those patients with chronic hepatitis or compensated cirrhosis of liver received Sofosbuvir 400 mg and Daclatasvir 60 mg for 12 weeks and those with decompensated cirrhosis of liver received the both the drugs for 24 weeks. HCV RNA levels were measured at the beginning of the treatment, end of treatment and 12 weeks after completion of treatment.

Results: 30 patients (22M: 8F) with a mean age of 47±8 years were included, of which 13 (43.3%) had cirrhosis of liver. Of the 13 Cirrhotic patients 9, 3, and 1 were in CTP A, B and C stage respectively. Among the total patients 23(76.7%), 5(16.7%), 2(6.7%) were genotype 3, 1 and 4 respectively .Three patients were treatment failure (previously treated with IFN and RBV combination), two were post renal transplant and one was a hemophilia patient. Median Viral load was: 499801 IU/ml (range: $2.4x10^3$ -$7.1x10^8$), Median viral load in chronic hepatitis C patients and cirrhosis of liver patients were $2.8x10^6$ and $1.3x10^6$ IU/ml respectively. Overall ETR and SVR were 100% in patients across the genotype. No significant adverse reactions were observed.

Conclusion: Combination treatment with Sofosbuvir and daclatasvir is very effective in chronic hepatitis patients with or without cirrhosis of liver, across the genotypes (Genotypes 1, 3 and 4)

Keywords: Hepatitis C; Genotype; SVR; sofosbuvir; daclatasvir.

1. Introduction

Hepatitis C virus (HCV) infection has an estimated global prevalence of 2%–3%, with approximately 122–185 million HCV-infected persons worldwide [1-7]. Prevalence of HCV infection in India has been variously estimated as 0.9 and 1.9% [8-9]. Since India has one-fifth of the world's population, with either of these estimates, it would account for a large proportion of the worldwide HCV burden. Blood bank data form the largest source of data on prevalence of HCV in India. In these data, anti-HCV prevalence was 0.29%–1.85% in northern states, 0.08%–1.4% in southern states, 0.27%–1.17% in northeastern states and 0.31– 1.09% in eastern states [10-17]. Genotype 3 is the most common HCV genotype in India, followed by genotype 1[18-26]. Genotype 1 has been reported more commonly from southern India than from other parts of the country and there are increasing reports of genotype 4 from India [27-28].

The primary goal of HCV therapy is to cure the infection. A sustained virological response (SVR) is defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion. The infection is cured

in more than 99% of patients who achieve an SVR. Patients with cirrhosis remain at risk of life-threatening complications; however hepatic fibrosis may regress and the risk of complications such as hepatic failure and portal hypertension is reduced [29].

Until 2011, the combination of pegylated interferon (PegIFN)- a and ribavirin for 24 or 48 weeks was the approved treatment for chronic hepatitis C . With this regimen, patients infected with HCV genotype 1 had SVR rates of approximately 40% in North America and 50% in Western Europe [30-33].

The treatment of hepatitis C virus has changed dramatically with the rapid advent of numerous new antiviral agents, especially direct-acting antivirals. Given the better safety profile and high antiviral potency of direct-acting antivirals, their combination in interferon-free oral regimens is becoming the standard of care for hepatitis C virus infection, tailored to individual patients according to the degree of disease progression (fibrosis), hepatitis C virus genotype and subtype, resistance profile, and prior therapeutic history[34].

Results from clinical studies as well as preliminary real-life data regarding the combination of sofosbuvir (a nucleotide polymerase inhibitor) and daclatasvir, a first-in-class NS5A replication complex inhibitor, demonstrate that it is one of the most promising antiviral therapies, with once-daily oral dosing, a low pill burden, good tolerability, and limited drug–drug interactions, in addition to high antiviral potency, with 90% sustained virologic response rates. This combination has high pangenotypic antiviral potency regardless of the severity and patient characteristics. The combination of sofosbuvir and an NS5A inhibitor with ribavirin for 12 weeks appears to be a very good further treatment option in both cirrhotic and treatment-experienced patients whatever the stage of fibrosis.[34]

Newer guidelines published by the AASLD and EASL cannot be applied in India as most of the drugs have not been marketed in India. Another factor to be considered is that the most common genotype in India is genotype 3 and studies in the west have not shown a satisfactory response to DAA. INASL had formulated guidelines for treatment of HCV according to the available drugs which initially included interferon and ribavirin. After Sofosbuvir and Daclatasvir became available in 2015, guideline was revised. Current guideline recommends use of sofosbuvir and daclatasvir for 12 weeks in non cirrhotics and 24 weeks in cirrhotics with ribavrin.[40] Drug compliance is an important issue in countries like india. There are studies from the west which shows the efficacy of Sofosbuvir-Daclatasvir combination without ribavirin[34]. Studies comparing the efficacy of DAA are lacking in India, and treatment response among Indian patients is not published. The aim of the study is to assess pan genotypic response to combination treatment with Sofosbuvir and Daclatasvir in chronic hepatitis C patients.

2. Materials and methods

All chronic hepatitis C patients attending the department of Gastroenterology, Calicut Medical College, Kozhikode, Kerala, India were included in the study. Exclusion criteria included all patients with hepato cellular carcinoma, patients with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy; pregnant patients and patients with seizure disorder who are on anti convulsants. The study was conducted in accord with the ethical principles that originated in the Declaration of Helsinki, and the study protocol was approved by the institutional research committee and independent ethics committee.

A detailed history will be elicited including initial presentation, disease duration, complications, extra hepatic manifestations, co-morbidities, drug history, previous treatments for HCV, its response and current status. A detailed physical examination including the vitals, BMI, signs of chronic liver disease and systemic examination. Lab tests like complete blood count, renal function test, liver function test, electrolytes, blood sugar levels, urine routine examination and chest X - ray were be taken.

HIV, HBsAg and IgM anti HCV were be done as part of the etiological and prognostic work up of CLD.USG abdomen and Esophago gastro duodenoscopy were done as part of characterization of liver disease.

Stage of the liver disease (chronic hepatitis or cirrhosis stage) assessed by clinical, biochemical, endoscopic and imaging studies. Sofosbuvir 400mg and Daclatasvir 60 mg once daily (QD) for 12 weeks were given to all patients with chronic hepatitis or compensated cirrhosis. Those with decompensated cirrhosis were treated with Sofosbuvir 400mg and Daclatasvir 60 mg once daily (QD) for 24 weeks. Patients were monitored at 4 weeks, 8 weeks, 12 weeks and 24 weeks.

ETR (End of treatment response) was assessed on completion of treatment for recommended period by assessing the HCV RNA PCR values. Sustained virological response (SVR) was assessed at 12 weeks after completion of treatment.. Factors influencing the SVR and any significant adverse effects related to the DAAs in study population were assessed.

2.1 HCV RNA Quantification and Genotyping

Pre treatment assessment of quantitative HCV RNA levels and HCV genotype were assessed. Plasma HCV RNA was analyzed by using the COBAS Ampli-

Prep/COBAS TaqMan HCV Test, HCV viral load expressed as IU/ml. The lower limit of detection of the assay was 15 IU/ml. The COBAS AmpliPrep/COBAS TaqMan HCV Test is an in vitro nucleic acid amplification test for the quantitation of hepatitis C viral (HCV) RNA in human plasma or serum of HCV-infected individuals using the COBAS AmpliPrep Instrument for automated specimen processing and the COBAS TaqMan Analyzer or the COBAS TaqMan 48 Analyzer for automated amplification and detection. Specimens containing HCV genotypes 1 - 6 have been validated for quantitation in the assay.

HCV genotyping is done by Nested RNA Polymerase Chain Reaction. This test is designed to detect four clinically relevant HCV genotypes (i.e. HCV type 1, 2, 3 & 4). Non-typeable results could be obtained due to one of the following reasons: 1) HCV viral load is very low (generally below 6,000 copies /ml). 2) HCV sequence divergence preventing amplification primers from hybridizing (generally due to mutations).

SVR12 is defined as HCV-RNA levels <LLOQ (lower limit of quatitation) either detectable or undetectable)

2.2 Statistical analysis

Data entered in Microsoft excel spread sheet and analyzed statistically using SPSS (Statistical Programme for Social Science) software for windows. Data analyzed using appropriate statistical tests. Quantitative data analyzed using‘t test’ and Qualitative data using Chi square test. Significance of association analyzed by calculating ‘p ‘value

3. Results

A total of 30 patients were included in the study. 22Male: 8Female with a mean age of 47±8 years were studied. Three patients were prior treatment failure (previously treated with PEG-IFN α and RBV combination), two were post renal transplant and one was a hemophilia patient. IV drug abuse was a definite risk factor in 14% of the patients. 43.3 % (13 patients) had cirrhosis of liver. 30% (9 patients) had CHILD A cirrhosis, 10% of the patients had CHILD B cirrhosis while only one patient had CHILD C cirrhosis at the time of the study. Most common genotype was HCV genotype 3 (76%), followed by genotype 1 (16%) and least common was genotype 4 (6%). Among the previously treated patients, two were of genotype 3 and one was genotype 1b. Of the 23 patient infected with genotype 3, 6(26%) patients had Child A cirrhosis, 3 (13.3%) patients had Child B cirrhosis while only one had Child C cirrhosis. Median Viral load was: 499801 IU/ml (range: 2.4 x 10^3 -7.1 x 10^8), Median viral load in chronic hepatitis and cirrhosis of liver patients were 2.8x10^5 and 1.3x10^6 IU/ml respectively. Overall ETR and SVR were 100% in patients across the genotype (Genotype 1,3 and 4).Patients who failed on Interferon and ribavirin were also achieved SVR12. No significant adverse reactions were observed.

Table 1: Demographic profile of patients

Demographic Profile		
	Male	**Female**
Number of patients	**22**	**8**
Age (years)	45±14 (73%)	50±16 (27%)
HCV RNA (median)	5.9log±2.0	5.3log ± 3.8
Chronic Hepatitis	11	6
Cirrhosis	11	2
Risk Factors		
IV drug abuse	3(14%)	0
Blood transfusion	4(18%)	1(12.5%)
Surgery	4(18%)	4(50%)
Hemodialysis	2(9%)	1(12.5%)
Co morbidities		
Diabetes	8(26%)	2(6.7%)
Obesity	9(30%)	8(26%)

Table 2: Log HCV RNA vs Stage of liver disease

Log HCV RNA	Stage of liver disease				Total
	Chronic Hepatitis	Child A	Child B	Child C	
3.00	2 (6.7%)	1 (3.3%)	0	0	3 (10.0%)
4.00	3 (10.0%)	1 (3.3%)	3 (10.0%)	0	7 (23.3%)
5.00	5 (16.7%)	1 (3.3%)	0	0	6 (20.0%)
6.00	5 (16.7%)	6 (20.0%)	0	0	11 (36.7%)
7.00	1 (3.3%)	0	0	1 (3.3%)	2 (6.7%)
8.00	1 (3.3%)	0	0	0	1 (3.3%)
Total	17 (56.7%)	9 (30%)	3 (10%)	1 (3.3%)	30

Figure 1: Sex of patients vs log HCV RNA

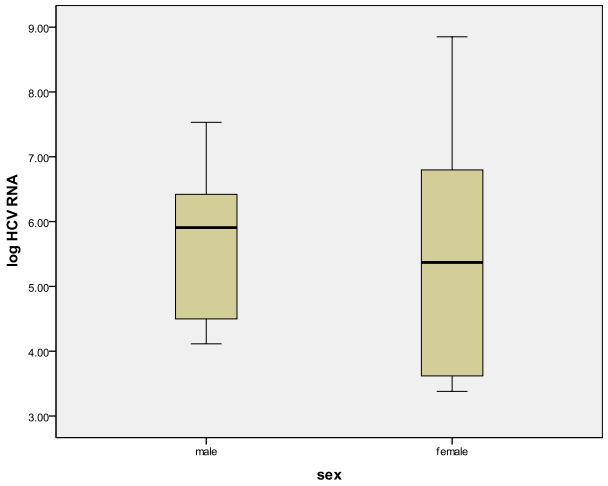
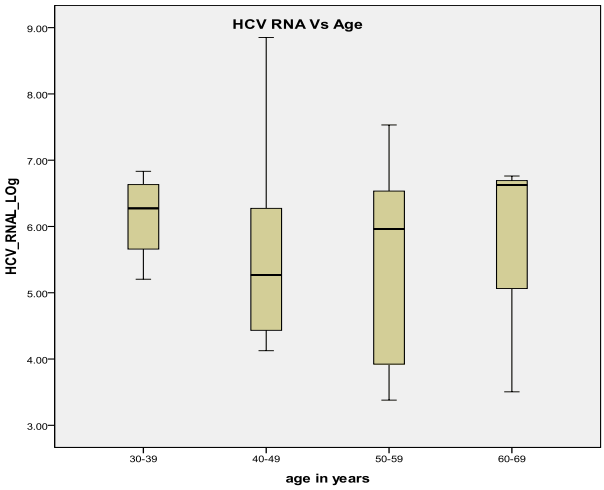


Figure 2: Age of patients vs log HCV RNA



4. Discussion

The study had a total of 30 subjects; 56% of the patients did not have cirrhosis of liver whereas 30% (9 patients) had CHILD A cirrhosis, 10% of the patients had CHILD B cirrhosis while only one patient had CHILD C cirrhosis at the time of the study. Most common genotype was HCV genotype 3 (76%), followed by genotype 1 (16%) and least common was genotype 4 (6%). Of the 23 patient infected with genotype 3, 6(26%) patients had Child A cirrhosis while only one had CHILD C cirrhosis. In patients without cirrhosis, median HCV RNA level was $2.8x10^5$, while in CHILD A cirrhosis patient's median RNA level was $1.6x10^6$ IU/ml. Only one patient had CHILD C cirrhosis with HCV RNA level of $1x10^7$ IU/ml. 100% of the patient achieved end of treatment response and SVR at 12 weeks.

In the first study by Sulkowski MS *et al* comparing the efficacy of Sofosbuvir and Dacltasvir in chronic HCV infection, 98% of patients infected with genotype 1 achieved SVR at 12 weeks, while those with genotype 3 infection had an SVR rate of 89%[35]. In genotype 1-infected patients, the SVR12 rate was 98%, regardless of viral subtype (genotype 1a 98%; genotype 1b 100%), interleukin-28B genotype (CC genotype 93%, non-CC genotype 98%), race (white 97%, black 96%, other 90%), ribavirin status (yes 94%, no 98%), or prior history of treatment (non-responders to protease inhibitors 98%). These high SVR rates also occur irrespective of duration of therapy (12 vs 24 weeks) in treatment-naïve patients Absence of cirrhosis was an important factor in achieving SVR especially in patients with genotype 3 infection. In our study 76% of the patients had genotype 3 infection and 44% of the patients had cirrhosis. All the patients achieved SVR at 12 weeks despite of the underlying severity of liver disease.

The ALLY- 3 study enrolled 101 patients with genotype 3 infections to receive open label Daclatasvir and sofosbuvir for 12 weeks. SVR 12 was achieved in 90.1% and 86.3% of the treatment naïve and treatment experienced patients. SVR at 12 weeks was 65% in 21% of the cirrhotic patients as compared to the non cirrhotic patients included in the study. SVR rate in our study was 100% as compared to ALLY-3 trial [36]. In our study 44% of the cirrhotic patients had genotype 3 infection and 3(10%) patients had previously been treated with interferon and ribavirin.

Pol S *et al* assessed safety and efficacy of the combination daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients from the French observational cohort ANRS CO22 HEPATHER. Sofosbuvir + daclatasvir + ribavirin for 12 weeks achieved a 100% SVR4 rate in patients with cirrhosis, with no additive effect on extension of treatment to 24 weeks with or without ribavirin (95.7% and 92.5%, respectively) and this was also true in experienced patients[37]. Decompensated cirrhotic patients in our study achieved SVR12 with 24 weeks treatment with sofosbuvir and daclatavir combination without ribavirin.

Most recently, preliminary reports given by Buggisch JP *et al* from the SOFGER Trial showed that with the sofosbuvir + daclatasvir combination without ribavirin for 12 weeks, 84% of the 161 patients who reached follow-up week 4, mostly difficult-to-treat patients (prior non-responders and cirrhotics) achieved an SVR4[38].

In the ALLY-3 HCV RNA level > $2x10^7$ was observed to be a risk factor for treatment failure [36]. In the present study patients without cirrhosis had a mean HCV RNA level $4x10^7$ IU/ml, while in CHILD A cirrhosis mean RNA level was $2x10^6$ IU/ml and CHILD C cirrhosis RNA level was $1x10^7$ IU/ml. Our study showed that even with RNA levels more than 7log10, it is possible to achieve SVR at 12 weeks in both cirrhotic and non cirrhotic patients. There was no worsening of the underlying liver disease during the treatment.

All patients tolerated the drugs without any significant side effects. Headache, nausea and fatigue were the minor side effects which were present in more than 5% of patients.

The observations from our study shows that sofosbuvir and daclastvir combination is very effective patients with chronic hepatitis C infection. The combination can achieve SVR 12 in patients with chronic hepatitis/compensated cirrhosis and decompensated cirrhosis with 12 and 24 weeks of treatment. The drawbacks of our study is that the total number of patients is less; probably leading to an SVR rate of 100%. Further studies are needed to demonstrate the efficacy of the drugs but this study is the initial step. Thus the all oral short course treatment will bring the cost of treatment to an affordable rate especially in developing country like India.

5. Conclusion

Combination treatment with Sofosbuvir and daclatasvir is very effective in chronic hepatitis patients with or without cirrhosis of liver, across the genotypes (Genotypes 1, 3 and 4)

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