



Sofosbuvir and Daclatasvir Bypassing Genotypic Investigation of Chronic Hepatitis C Infection: A Real-Life Experience at Tertiary care center in North Indian Population

Sofosbuvir and Daclatasvir Bypassing Genotypic Investigation

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Abstract

Background and Aims: The goal of Hepatitis C Virus infection treatment is to remove the virus, to avoid advancement of Hepatitis C Virus (HCV) infection and progression of related disease such as liver cirrhosis and hepatocellular carcinoma and to achieve End of Treatment Response (ETR) with 12-week therapy and Sustained Virological Response (SVR) at post-treatment week 12 (SVR-12), which is defined as undetectable HCV RNA at 12 weeks post ETR. In the Compassionate Use Program (CUP) in Europe, Sofosbuvir (SOF) and Daclatasvir (DCV) were used in all genotypes and achieved SVR-12. **Aims:** Our aim is to compare the efficacy and effectiveness of Sofosbuvir and Daclatasvir in the treatment of HCV infection in the patients who could not afford for the investigating of HCV-Genotype and to those in whom genotyping was done. **Methods:** Group 1 includes ten patients, given Sofosbuvir and Daclatasvir without genotype and group 2 includes nine patients, given Sofosbuvir and Daclatasvir with genotype. The patient group selection was done using a randomized table generated by using excel. All the patients in the groups completed the twelve weeks treatment with twelve weeks and twenty-four weeks of follow up. All the nineteen patients were given Sofosbuvir and Daclatasvir for twelve weeks and the endpoint of therapy was marked by undetectable HCV-RNA in blood by ETR-12 (end of treatment response), Sustained Virological Response at post-treatment week 12 (SVR-12) and Sustained Virological Response at post-treatment week 24 (SVR-24). **Results:** Quantitative HCV-RNA (IU/ml) by RT-PCR was undetectable in all the patients in both groups at the end of treatment (ETR-12) and SVR-12- and SVR-24-weeks follow-up after completion of treatment i.e. Sofosbuvir and Daclatasvir has 100% ETR-12, SVR-12 and SVR-24 in both the groups. **Conclusion:** If patients do not investigate for genotype and use the Sofosbuvir and Daclatasvir in HCV infected patients, there is no effect on outcome ETR. This will reduce the risk of late stage complications such as liver cirrhosis and hepatocellular carcinoma and will also leads to the economic benefits such as no extra burden on patients.

Keywords: Cirrhosis, End of Treatment Response (ETR), Hepatocellular Carcinoma (HCC), Sofosbuvir and Daclatasvir (SOF+DCV), Steatosis, Sustained Virological Response (SVR)

1. Background

Hepatitis C Virus (HCV) is a positive-strand RNA virus of the Flaviviridae family and contains a single-stranded RNA genome of approximate 9600 nucleotides and is a globally prevalent pathogen and also a major cause of healthcare burden in India. HCV infection is a significant problem in India. HCV has six major genotype 1 to 6, genotype 1 is the most prevalent

genotype globally (46%), followed by genotype 3 in 22% and genotype 2 and 4 in 13% each and there is a significant genotypic variation across various geographic regions globally. While genotype 1 predominates in Europe, North America and Australia, genotype 3 is more prevalent in Asian countries such as India, Pakistan and Bangladesh. HCV is the disease that has affected around 200 million people globally¹. End-stage Liver Disease (ESLD) due to chronic hepatitis C infection remains

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the leading cause for liver transplantation, placing a major burden on health care services^{2,3}. Although, the impact of HCV heterogeneity and genotypes on the clinical management of chronic HCV infection has not been established and its role as an epidemiologic marker has been clearly shown. The sensitiveness of serologic and virologic assays for the detection of HCV may be influenced by the heterogeneity of HCV. However, the accurate role of genotypes in the progression of liver disease, the outcome of HCV infection, and the response to the antiviral therapy are much less well understood than their role as an epidemiologic marker. In India the most prevalent genotype is 3 with subtype 3a and 3b^{4,5}. In the Indian scenario, due to the absence of a HCV surveillance system in India, there is a lack of knowledge about the actual number of people living with HCV-related liver diseases and the people who died because of it. The calculated prevalence of HCV infection in India is about 1–1.9%⁶ although variations have been reported in literature across various geographical regions in India. The disease is most prevalent in Punjab, Haryana, Andhra Pradesh, Puducherry, Arunachal Pradesh and Mizoram. An official statement is released by the Delhi-based Institute, Institute of Liver and Biliary Science (ILBS) in 2014, highlighted the number of people living with chronic Hepatitis C infection, which was approximately 12 million. HCV infection is just one part of the complete burden of viral hepatitis in India and is the blood-borne and can be transmitted from one human to another⁷. Oral combinations of Direct-acting Antivirals (DAAs) have become the standard of care for the treatment of chronic HCV infection^{8–11}. In clinical trials, the rates of sustained virological response at post-treatment week 12 (SVR12) exceeding 90% have been reported for several drug combinations, with safety profiles superior to those of peg interferon-based regimens. Daclatasvir (DCV) is a potent, pan-genotypic inhibitor of the HCV NS5A protein; Sofosbuvir (SOF) is a pan-genotypic nucleotide analogue inhibitor of the HCV NS5B RNA polymerase^{12,13}. In the phase III drug trial studies, the 12-week, once-daily oral combination of DCV and SOF, with or without ribavirin (DCV+SOF±RBV), was well tolerated and achieved SVR12 rates exceeding 90% in patients who have been challenging to treat effectively, including those with advanced cirrhosis, HIV/HCV co-infection, HCV genotype 3 infection and HCV recurrence after liver transplant^{14–16}.

2. Methods

2.1 Patients and Treatment

It was an observational study conducted from February 2017 to December 2017 at the outpatients of Medical Gastroenterology unit of medicine department. A favorable ethical opinion [Ref. no: 103/Ethics/R.Cell-17, Dated: 22/08/2017] was obtained

from the King George's Medical University ethical committee [Registration no.: ECR/262/Inst/UP/2013/RR-16] for the study. A total of 19 patients with mean age of 38.6±8.4 years, were enrolled after informed consent. HCV infection was confirmed by 3rd generation ELISA and patients with chronic infection of HCV, confirmed with detectable HCV-RNA in IU/ml (quantitative analysis) with a genotype 3 by RT-PCR, were included in the study. These patients were categorized into 2 groups. Group 1 includes 10 patients, given Sofosbuvir and Daclatasvir without genotype and group 2 include 9 patients, given Sofosbuvir and Daclatasvir with genotype 3. Those with the features of decompensated liver disease such as ascites, variceal bleeding or portosystemic encephalopathy and those with comorbid conditions such as positive hepatitis B surface antigen, positive HIV (Human Immunodeficiency Virus), other chronic liver diseases i.e., alcoholic liver disease, hepatotoxic drugs, autoimmune chronic hepatitis, treatment experienced patients and hemochromatosis were excluded from the study. Using Graph Pad Prism software package carried out all statistical analysis and unpaired student's t-test was employed to compare numerical variables between patients with or without genotype.

2.2 Laboratory Methods

HCV viral load was measured using real time PCR as per protocol described by¹⁷. HCV RNA positive samples were genotyped using core region, as described by¹⁸ with slight modifications. Real Time PCR with lower limit of detection of 20 IU/mL. Absence of detectable HCV RNA using this assay at different time points was used to define ETR, SVR-12 and SVR-24.

3. Results

A total nineteen patients consented to begin the therapy and the study will be categorized into two groups. Group 1 included ten patients, given Sofosbuvir and Daclatasvir without investigating genotype with the mean age group of 41.2±11.5 and the group 2 included nine patients, given Sofosbuvir and Daclatasvir with genotype 3, with the mean age group of 38.6 ± 8.4 4 years are summarized in table 1 and table 2¹⁹. All the patients completed the 12 weeks treatment (ETR 12), 12 weeks follow up SVR-12 and SVR-24. HCV RNA was undetectable in all the patients in both groups at the ETR and SVR-12 (100% ETR-12 and SVR-12 and SVR-24 achieved in both the groups).

3.1 Follow-up (ETR-12 and SVR-12)

All patients underwent quantitative analysis of HCV-RNA at the end of treatment response (12 weeks i.e. ETR-12) and

Characteristics and outcomes of patient's baseline and follow-up characteristic are summarized as bellow:

Table 1. Comparison of baseline and follow-up treatment characteristic of group-1 (Without GT) patients¹⁹

Without GT (Group-1)						
Treatment SOF + DCV	Baseline		Follow-up Treatment		Unpaired t test	
Baseline Characteristic	Mean	SD	Mean	SD	P value	P value summary
Hb	13.3	2.1	13.7	1.8	0.6708	ns
PLT	192000	41923.21	215200	33522.1	0.1885	ns
Alb	4.8	0.6	4.8	0.7	0.8864	ns
AST	74.6	63.4	34.5	8.5	0.0628	ns
ALT	82.8	65.6	39.8	9.1	0.0549	ns
PT	13.6	0.7	14.2	0.4	0.0361	*

P value less than 0.05 considered as significant.

Table 2. Comparison of baseline and follow-up treatment characteristic of group 2 (With GT-3) patients¹⁹

With GT 3 (Group-2)						
Treatment SOF + DCV	Baseline		Follow-up Treatment		Unpaired t test	
Baseline Characteristic	Mean	SD	Mean	SD	P value	P value summary
Hb	11.6	1.8	12.1	2.0	0.5599	ns
PLT	190889	70029.4	222889	42345.1	0.2579	ns
Alb	4.0	0.5	4.0	0.4	0.8716	ns
AST	102.6	69.4	37.2	17.7	0.0146	*
ALT	97.3	93.2	37.4	13.6	0.0744	ns
PT	14.1	1.4	14.6	0.5	0.3755	ns

P value less than 0.05 considered as significant.

12 weeks after stopping the treatment (SVR-12). The ETR and SVR were determined for each patient with quantitative HCV-RNA of lower limit of detection as 20 IU/ml. ETR was defined as negative quantitative HCV-RNA at the end of treatment, while SVR was defined as negative quantitative HCV-RNA 12 weeks after the completion of therapy and all the patients achieved 100% ETR-12 and SVR-12 in both the enrolled groups. The outcomes of ETR-12 and SVR-12 of patients on Sofosbuvir and Daclatasvir combination therapy of both groups are summarized as below in (Table 3 and Table 4). All the patients achieved 100% ETR-12 and SVR-12 respectively.

3.2 Follow-up (SVR-24)

In group 1 (i.e. without GT, n = 10), total follow up patients were 7 and 3 patients were lost to follow up and all the follow up seven patients, underwent quantitative analysis of HCV-

Table 3. HCV-RNA at baseline, ETR-12 and SVR-12 without genotype¹⁹

Treatment Regimen Without GT (Group 1)	HCV-RNA at Baseline	ETR-12	SVR-12
SOF + DCV	10000	0	0
SOF + DCV	7300000	0	0
SOF + DCV	490000	0	0
SOF + DCV	110000	0	0
SOF + DCV	10000	0	0
SOF + DCV	10000	0	0
SOF + DCV	94000	0	0
SOF + DCV	60100	0	0
SOF + DCV	1093	0	0
SOF + DCV	15000	0	0

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Table 4. HCV-RNA at baseline, ETR-12 and SVR-12 with genotype¹⁹

Treatment Regimen With GT (Group 2)	HCV-RNA	ETR-12	SVR-12
SOF + DCV	6900000	0	0
SOF + DCV	93000	0	0
SOF + DCV	110000	0	0
SOF + DCV	9800000	0	0
SOF + DCV	160000	0	0
SOF + DCV	1400000	0	0
SOF + DCV	130000	0	0
SOF + DCV	17000000	0	0
SOF + DCV	3700000	0	0

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RNA at SVR-24 after stopping the treatment and found with a quantitative HCV-RNA of lower than detection limit (20 IU/ml). In group 2 (i.e. with GT, n = 9), total follow up patients were 8 and 1 patients were lost to follow up and all the follow up eight patients, underwent quantitative analysis of HCV-RNA at SVR-24 after stopping the treatment found lower than detection limit (20 IU/ml).

4. Discussion

We reported here our experience with DAA-based regimens for the treatment of CHC-3 infection. Hepatitis C Virus with genotype 3 has generally proven to be more challenging to treat with oral antivirals than other genotypes. This present study involved a small real-world cohort of patients with genotype 3 infection chronic liver disease provides data on the clinical effectiveness of Sofosbuvir and Daclatasvir in a challenging subset of patients with very limited treatment options. The result of this study suggests that overall ETR-12 and SVR-12 rates of 100% with and without investigating HCV Genotype. In a European CUP provided clinically relevant information on the effectiveness and safety of Sofosbuvir and Daclatasvir, with or without RBV, in a large cohort of patients with advanced liver disease and resulted in an overall SVR12 rate of 91%²⁰. Similar study demonstrated that high SVR12 rates were observed in patient subgroups with characteristics regarded as more difficult to cure, such as decompensated cirrhosis and genotype 3 infections with cirrhosis²⁰.

5. Conclusion

If patients do not investigate for genotype and use the Sofosbuvir and Daclatasvir in HCV infected patients, there is no effect on the outcome end of treatment response. Sofosbuvir

and Daclatasvir have shown to be very effective and successful treatment of the Hepatitis C Virus infection with achievement of virological response and have no resistance in HCV genotype 3 treatments in our study population. The promising results of our study will aid in better outcomes and therefore help in eradication of the Hepatitis C Virus.

6. Abbreviations

OPD: Out Patients Department, HCV: Hepatitis C Virus, HCC: Hepatocellular Carcinoma, BMI: Body Mass Index, Hb: Hemoglobin, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, PT: Prothrombin Time, Anti HCV: Hepatitis C Antibody, RNA Level: Ribo-nucleic Acid Level, HIV: Human Immunodeficiency Virus, HCV-Genotype: Hepatitis C Virus Genotype, ELISA: Enzyme-linked Immune Sorbent Assay.

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