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Research Article

# Combination Treatment of Sofosbuvir Plus Daclatasvir for 12 Weeks in HCV Genotype 3-Infected Bangladeshi Patients: Achievment of a Sustained Virological Response

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## Abstract

**Background:** Hepatitis C virus (HCV) is a major cause of chronic liver disease affecting close to 170 million people worldwide. All-oral combination therapy is desirable for patients with chronic hepatitis C virus (HCV) infection. 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. We evaluated daclatasvir (an HCV NS5A replication complex inhibitor) plus sofosbuvir (a nucleotide analogue HCV NS5B polymerase inhibitor) in patients infected with HCV genotype 3. The aim of the study is to evaluate the efficacy and treatment response of Sofosbuvir plus Daclatasvir in HCV patients with genotype 3.

**Materials and Methods:** A total 24 patients with genotype 3 were included in this study. Patients received tab sofosbuvir 400 mg plus tab daclatasvir 60mg daily for 12 weeks. Outcome was assessed at the end of 4 weeks (RVR), 12 weeks (EVR) and 24 weeks (SVR).

**Results:** Twenty four patients were recruited in this study. The study population comprised 50% male and 50 % female. Among them 29.2% were between 41-50 ages and 25% were between 31-40 ages. 37.5% patients complaints for loss of appetite. 79.2% were genotype 3b and 20.8% were genotype 3a. All patients received sofosbuvir (400 mg) and daclatasvir (60 mg) for 12 weeks. SVR12 100% were achieved in all of them.

**Conclusion:** All patients with genotype 3 achieved SVR12 100% after the completion of therapy with sofosbuvir and daclatasvir. The combination of sofosbuvir and an NS5A inhibitor for 12 weeks appears to be a very good further treatment option in patients with whatever the stage of HCV.

**Keywords:** Hepatitis C Virus; Antiviral Drugs; Sofosbuvir; Daclatasvir

## Introduction

Hepatitis C virus (HCV) is a major cause of chronic liver disease affecting close to 170 million people worldwide. Approximately 85% of patients acutely infected with HCV progress to chronic liver disease with persistence of HCV RNA for more than 6 months [1]. Among patients with chronic HCV infection, 15-20% progress to end-stage liver disease [2] and approximately 1-4% of these will develop hepatocellular carcinoma. Also, the prevalence of infection is highest among middle-aged patients and more of these patients will progress to cirrhosis or hepatocellular carcinoma with time [3]. With hepatitis C being a major health care concern, predicting the outcome of treatment in these patients becomes all the more important [4]. The HCV genotype is of clinical significance as it helps to tailor the treatment regimen and helps in monitoring response to treatment [5,6]. HCV is classified into six major genotypes with more than 50 known subtypes. Genotype 1 is the most common genotype present globally being predominantly found in America, Japan, Korea, Australia & New Zealand whilst genotype

3 is highly prevalent in the Indian subcontinent [6]. Genotype 4 is predominantly found in the Middle-East and Egypt Genotype 5 is commonly found in South Africa while genotype 6 is found in West Asia [5]. HCV genotype 3 is considered easy to treat. The pivotal trials show a response rate of 80% in patients with chronic HCV genotype 3 infection [7].

The treatment of hepatitis C virus has changed dramatically with the rapid advent of numerous new antiviral agents, 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. The primary efficacy end point was sustained virologic response, defined as the absence of detectable HCV RNA at the end of follow- up according to a PCR assay.

## Patients and Methods

### Study design and patients

The study was conducted in Department of virology, BSMMU. Eligible patients were between 15-70 years old were treatment naive had HCV-RNA levels ≥10,000 IU/mL at screening. T reatment –naïve patient had no previous exposure to any IFN formulation, RBV, or any anti-HCV direct acting antiviral (DAA) agents. Patients who received previous therapy with NS5A inhibitors and those who previously discontinued treatment with SOF plus RBV prematurely because of intolerance (other than exacer- bation of anemia) were excluded. The exclusion criteria were as follows: (1) severe anemia at baseline; (2) severe renal dysfunction at baseline; (3) presence of HCC; and (4) any serious medical condition of any other organ, such as arrhythmia or congestive heart failure. Patients with a history of curative treatment of HCC were included. All patients were genotype 3 received open-label treatment with DCV 60 mg plus SOF 400 mg once-daily for 12 weeks, with a subsequent 24-week follow-up. All patients provided written informed consent before participation in the study.

## Results

Demographic characteristics are shown in Table 1. Among 24 patients 50% were male and 50 % were female. 29.2% were between 41-50 years age. 37.5% patients were complaints for loss of weight and 29.2% with loss of appetite. 87.5% patients with normal upper endoscopic findings.

| | Number (Percentage) |
|---|---|
| Age | |
| 21-30 | 5 (20.8) |
| 31-40 | 6 (25.0) |
| 41-50 | 7 (29.2) |
| 51-60 | 3 (12.5) |
| 61-70 | 3 (12.5) |
| Sex | |
| Male | 12 (50) |
| Female | 12 (50) |
| Occupation | |
| Service | 7 (29.2) |
| Business | 3 (12.5) |
| Student | 2 (8.3) |
| Unemployed | 2 (8.3) |
| Housewife | 10 (41.7) |
| Travel History | |
| Yes | 4 (16.7) |
| No | 20 (83.3) |
| Chief Complaints | |
| H/O Jaundice | 2 (8.3) |
| Yellow | 1 (4.2) |
| Coloration | 4 (16.7) |
| Loss of wt | 9 (37.5) |
| Loss of appetite others | 7 (29.2) |
| System | 1 (4.2) |
| Marital History | |
| Married | 21 (87.5) |
| Unmarried | 3 (12.5) |
| UGI Upper endoscopy findings | |
| Normal | 21 (87.5) |
| Gastric | 2 (8.3) |
| System | 1 (4.2) |
| USG | |
| Normal | 15 (62.5) |
| Course echo-texture | 1 (4.2) |
| CLD | 2 (8.3) |
| Cirrhosis | 2 (8.3) |
| Hepatosplenomegaly | 1 (4.2) |
| Fatty liver | 3 (12.5) |

**Table 1:** Demographic characteristics of the 24 chronic HCV patients.

### Laboratory assessments

Blood samples were obtained at the baseline and weeks 4, 8 and 12 and then 4, 8 and 12 weeks after the end of treatment. HCV genotyping were performed as previously described [7]. HCV RNA was measured by COBAS TaqMan HCV assay version 2.0(Geneproof HCVRNA kit, Czech Republic) with a lower limit of quantification of 500 IU/mL. Rapid virological response (RVR) was defined as undetectable HCV RNA at week 4 after the start of treatment. End-of-treatment response (EOTR) was defined as undetectable HCV RNA at the end of treatment. SVR at 4, 8, or 12 weeks (SVR4, SVR8, or SVR12, respectively) was also used to evaluate the virological response.

### Treatment Response and Efficacy of Combination Treatment with Daclatasvir plus Sofosbuvir:

All 24 patients continued the combination treatment of Daclatasvir plus sofosbuvir for 12 weeks. During treatment rapid virological response (RVR) and end-of-treatment response( EOTR) rates were 83.3% and 100% respectively. After treatment the rate of SVR4, SVR8, and SVR12 were 99.2%, 98.3% and 100% respectively.

| Characteristics | All ( n= 24) Treatment-Naive |
|---|---|
| HCV undetectable no. (%) | |
| During treatment | |
| At 4 W | 19 (79.16) |
| At 8 W | 22 (91.66) |
| At 12 W | 24 (100) |
| After treatment | |
| Post 4 W | 22 (91.66) |
| Post 8 W | 24 (100) |
| Post 12 W | 24 (100) |
| Virological failure | 0 |
| Discontinutation | 0 |
| Relapse | 0 |
| Lost due to AEs | 0 |

**Table 2:** Response during and after treatment.

AEs, adverse events; w, weeks.

## Discussion

Sofosbuvir is an orally administered HCV nucleotide polymerase NS5B inhibitor. It is given once daily, and has a good safety profile [8,9]. Combination of sofosbuvir and daclatasvir with or without ribavirin has been well tolerated in previously treated or untreated HCV patients [10].

Daclatasvir is a first-in-class HCV NS5A replication complex inhibitor with pangenotypic activity and a pharmacokinetic profile allowing once-daily dosing. Reaching in vitro 50% effective concentrations ($EC_{50}$) in the picomolar range against HCV replicons representing six major HCV genotypes (1a, 1b, 2a, 3a, 4a, 5a), daclatasvir is one of the most potent HCV replication inhibitors reported to date [11]. Prospective studies thus far highlight the fact that younger age (age <40) is associated with more SVR [12-14]. The efficacy and safety of antiviral therapy in the older population is not clear and are limited to small, single-center studies [15,16 ].

A number of host, genetic and viral factors interact to predict the probable outcome of patients with HCV infection. HCV genotype other than 1 and low baseline viral load are the most important baseline predictors of SVR. RVR has become an important determinant of treatment duration irrespective of the genotype and the presence or absence of other determinants and has come to be recognized as one of the most powerful predictors of SVR. However, our understanding of the variable response in different patients is still unclear and more research is required to further elucidate the complex interactions between the virus and the host response.

The field of HCV treatment has changed dramatically with the advent of a number of new antivirals, including DAAs and agents with non-viral targets (cyclophilin inhibitors, IFN-lambda, vaccine therapy). Given their better safety profile and improved antiviral potency, combinations of these agents in IFN-free regimens are becoming the standard of care for HCV infection. All oral treatments will be tailored to individual patients according to the degree of disease progression (fibrosis), HCV genotype and subtype, resistance profile, and prior therapeutic history. Results from clinical studies as well as preliminary real-life data demonstrate that the combination of sofosbuvir and an NS5A inhibitor, including the first-in class agent daclatasvir, belongs to one of the most antiviral therapies with once-daily oral dosing, a low pill burden, good tolerability, and limited drug–drug interactions, in addition to high (.90%) SVR rates. Such a combination has pangenotypic high antiviral potency. Regardless of the severity of the underlying liver disease and the baseline characteristics of the patients, combination of sofosbuvir with an NS5A inhibitor for 12 weeks appears to be a very good option when used in combination with ribavirin in cirrhotic and treatment-experienced patients whatever their fibrosis stage. Future challenges to be addressed, over and above the already increased efficacy, will be to further improve the safety, adherence, and costs of these new oral combinations, particularly in patients with chronic renal failure or transplantation and in

complex clinical settings. Beyond the competition between companies, the next step is to improve screening and access to these therapies, which have shown good safety and efficacy for most patients. chronic infection with hepatitis C virus (HCV) genotype 3 is common throughout the world and remains a significant disease burden for many patients.1,2 Infection with HCV genotype 3 has been associated with an increased risk of progression to cirrhosis, as well as development of steatosis or hepatocellular carcinoma (HCC), compared with other HCV genotypes.3-5. Recent advances have led to the approval of interferon (IFN)-free and/or ribavirin (RBV)-free therapies for chronic infection with HCV genotypes 1, 2, 3, and 4. However, for both treatment-na€ıve and treatment-experienced patients with genotype 3 infection, IFN- and RBV-free therapy options are currently limited.

Virologic breakthrough and relapse were rare in our population and were not observed in any of the 24 patients infected with HCV genotype 3. Sofosbuvir-resistant variants were not detected in any of the patients. Our observations suggest that the development of resistance is uncommon with daclatasvir plus sofosbuvir.

## Conclusion

In conclusion, once daily, oral treatment with the NS4A inhibitor daclatasvir plus the NS5B polymerase inhibitor sofosbuvir was associated with high rates of sustained virologic response in untreated patients infected with genotype 3. Sofosbuvir plus daclatasvir was higly effective in Asian patients with an overall SVR12 rate of 100% and no Asian patients experiencing virologic failure. This regimen was well tolerated among Asian patients with no one prematurely discontinuing treatment due to AEs.

## Bibliography

1. National Institutes of Health. Consensus Development Conference on Hepatitis C". *Hepatology* 36 (2020): S3-S120.

2. Liang TJ., *et al*. "Pathogenesis, natural history, treatment, and prevention of hepatitis C". *Annals of Internal Medicine* 132 (2000): 296-305.

3. Armstrong GL., *et al*. "The prevalence of hepatitis C virus infection in the United States, 1999 through 2002". *Annals of Internal Medicine* 144 (2006): 705-714.

4. Centers for Disease Control and Prevention. Hepatitis Surveillance Report No. 60. Atlanta, US Dept of Health and Human Services, Centers for Disease Control and Prevention (2005).

5. Yu ML and WL Chuang "Treatment of chronic hepatitis C in Asia: when East meets West". *The Journal of Gastroenterology and Hepatology* 24.3 (2009): 336-345.

6. Narahari S., *et al*. "and geographic distribution of Hepatitis C Virus genotypes in Indian patient cohort". *Infection, Genetics and Evolution* 9.4 (2009): 643-645.

7. Manns MP., *et al*. "Peginterferon alfa-2b plus ribavirin compared with interferon alfa- 2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial". *Lancet* 358.9286 (2005): 958-965.

8. Sofia MJ., *et al*. "Discovery of a beta-d-2′-deoxy-2′-alfafluoro-2′-beta-C-methyluridine nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus". *Journal of Medicinal Chemistry* 53.19 (2010): 7202-7218.

9. Gane EJ., *et al*. "Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C". *The New England Journal of Medicine* 368.1 (2013): 34-44.

10. Sulkowski MS., *et al*. "Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection". *The New England Journal of Medicine* 370.3 (2014): 211-221.

11. Gao M., *et al*. "Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect". *Nature* 465.7294 (2010): 96-100.

12. Shiffman ML., *et al*. "Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3". *The New England Journal of Medicine* 357 (2007a): 124-134.

13. Fried MW., *et al*. "Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection". *The New England Journal of Medicine* 347 (2002): 975-982.

14. Manns MP., *et al*. "Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial". *Lancet* 358 (2001): 958-965.

15. Koyama R., *et al*. "Necessities of interferon therapy in elderly patients with chronic hepatitis C". *Intervirology* 49 (2006): 121-126.

16. Terranova R and Luca S. "Preliminary results of beta-interferon treatment in the elderly". *Controlled Clinical Trials* 17 (1996): 123-129.