Safety and Efficacy of Sofosbuvir and Daclatasvir for Hepatitis C Virus Infection in Patients with β -Thalassemia Major

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Background and Aims: β -thalassemia major patients are susceptible to Hepatitis C Virus (HCV) infection owing to life-long dependency for blood-transfusion. Moreover, this patient population is at risk of progression of liver fibrosis or development of cirrhosis as a consequence of both iron overload and HCV infection. Hence, this study was carried out to evaluate efficacy and safety of the combination regimen of sofosbuvir and daclatasvir for HCV infection in β -thalassemia major patients. **Methods:** The present study was a prospective observational study which enrolled multi-transfused β -thalassemia major patients treated with a combination regimen of sofosbuvir (400 mg) and daclatasvir (60 mg) daily for 12 weeks for HCV infection during May 2016 and November 2016 depending upon inclusion and exclusion criteria of the study. Sustained virological response at post-treatment week-12 (SVR-12) was defined as negative HCV-RNA at week-12 after completion of antiviral treatment. **Results:** A total of 10 multi-transfused patients with β -thalassemia major were included in the study. Average age of the patient was 13.60 ± 4.38 years. All the included patients were treatment-naïve, non-cirrhotic and infected with HCV genotype-3. All the patients achieved SVR-12. There was significant reduction in aspartate aminotransferase ($p = 0.005$) and alanine aminotransferase level ($p = 0.005$) and serum ferritin level ($p = 0.028$) after completion of the antiviral treatment. The reported adverse events include nausea, vomiting and anorexia which were managed conservatively. None of the patient required dose reduction or termination of antiviral treatment. **Conclusion:** The study reports safety and efficacy of sofosbuvir-based treatment in non-cirrhotic, treatment-naïve β -thalassemia major patients infected with HCV genotype-3. However, further studies with larger patient populations are needed to build up stronger evidence of safety and efficacy of this treatment approach for HCV infection in thalassemic patients. (J CLIN EXP HEPATOL 2018;8:3-6)

See Editorial on Pages 2-3.

β -thalassemia, one of the most common inherited single gene disorder, is caused by point mutation or rarely deletion of β -globin gene on chromosome-11.¹ Due to life-long dependency for blood-transfusion, β -thalassemia patients are susceptible to transfusion-transmitted Hepatitis-C Virus (HCV) infection. Worldwide, 4.4% to 85.4% of thalassemia patients are found to

be positive for anti-hepatitis C antibodies.² Large number of blood-transfusions also lead to iron overload in these patients. Both HCV infection and iron overload are independent but mutually reinforcing risk factors for progression of liver fibrosis as well as development of cirrhosis in thalassemia patients.³ Hence, an effective antiviral treatment for HCV infection along with controlled iron overload in thalassemia patients may limit progression of liver impairment.^{3,4}

The emergence of Directly Acting Antivirals (DAAs) revolutionized treatment of HCV infection. Hence, DAAs seem ideal candidates to eradicate HCV infection and to improve prognosis of thalassemic patients. Sofosbuvir (SOF), a second generation DAA, is a selective pangenotypic nucleotide inhibitor of NSSB-directed HCV RNA replication. It has become the backbone of HCV treatment in international guideline.⁵ Moreover, the safety and efficacy of SOF-containing regimens has been proved in real life settings enriched with more elderly, treatment-experienced patients as well as patients with advanced fibrosis stages.⁶⁻⁸ However, to the date, there is scarcity of evidences demonstrating safety and efficacy of SOF-containing regimens in patients with β -thalassemia major.^{9,10} Hence, this

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Abbreviations: DAA: Direct Acting Antiviral; DCV: Daclatasvir; ETR: End of Treatment Response; HCV: Hepatitis C Virus; PegINF- α : Pegylated Interferon- α ; RBV: Ribavirin; RVR: Rapid Virological Response; SOF: Sofosbuvir; SVR12: Sustained Virological Response Post-treatment Week-12
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study was designed to evaluate safety and efficacy of combination regimen of SOF and Daclatasvir (DCV) for chronic HCV infection in patients with β -thalassemia major.

PATIENTS AND METHODS

Study Design and Patient Population

The current study was a prospective observational study which enrolled β -thalassemia major patients treated with SOF-based therapy for HCV infection during May 2016 and November 2016. The inclusion criteria of the study are (1) β -thalassemia major patients diagnosed with chronic HCV infection based on detection of HCV RNA in serum or plasma; and (2) if they were treated with full-dose of SOF (400 mg) and DCV (60 mg) daily for 12 weeks for HCV infection during study period. However, this study excluded the patients with decompensated liver disease, hepatocellular carcinoma, coinfection with hepatitis B virus and/or human immunodeficiency virus. Patients who were treated with amiodarone were also excluded.

All patients underwent clinical evaluation for past medical or surgical history, associated illnesses and concomitant medications. Each patient underwent complete blood count, liver and renal function tests, serum ferritin levels, abdominal sonography and transient elastography. HCV viral load and genotype were also determined using reverse transcription polymerase chain reaction assay (COBAS TaqMan HCV Test v. 2.0; Roche Molecular Systems, West Sussex, UK) with lower limit of quantification of 15 IU/mL. Virological response (HCV RNA level) was assessed at baseline, at week-4 of treatment, end-of treatment and at week-12 after cessation of the treatment. All the patients had been receiving blood-transfusion two to three times per month along with regular therapy with oral iron-chelating agent (desferrioxamine) before initiation of antiviral treatment. No change was made in their treatment of β -thalassemia. All the patients received 400 mg SOF and 60 mg DCV daily for 12 weeks. The patients were followed-up weekly for the assessment of adverse events.

The efficacy of the treatment was assessed based upon achievement of Sustained Virological Response at Post-treatment Week-12 (SVR-12), defined as negative HCV RNA (documentation of HCV RNA < 15 IU/mL) at 12 weeks after cessation of the treatment. Rapid Virological Response (RVR) was defined as undetectable HCV RNA (documentation of HCV RNA < 15 IU/mL) at week 4 of the treatment. End of treatment response (ETR) was defined as undetectable HCV RNA (documentation of HCV RNA < 15 IU/mL) at the end of treatment. Reappearance of HCV RNA (documentation of HCV RNA > 15 IU/mL) in patient who had ETR was considered as virological relapse. Occurrence of adverse events was noted as reported

by the patients or on the basis of abnormal laboratory findings.

The study was approved by institutional review board. This study was conducted in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Statistical Analysis

Descriptive analysis was performed and data are reported as mean $\pm$ standard deviation, median (interquartile range) or proportions (percentages) as appropriate for the level of measurement and distribution of the variables. Wilcoxon Rank test was performed to compare pre-treatment and post-treatment laboratory variables. Statistical analysis was performed using Statistical Package for Social Science (SPSS; Chicago, IL, USA) program, version 20.

RESULTS

Ten multi-transfused patients with β -thalassemia major who were treated with a full-dose of SOF (400 mg) and DCV (60 mg) daily for 12 weeks were included in this prospective study. Average age of the patient was 13.60 $\pm$ 4.38 years. All the included patients were treatment-naïve, non-cirrhotic and infected with genotype-3. None of the included patient developed cirrhosis or had a history of splenectomy. The demographic and baseline clinical characteristic of the patient has been depicted in Table 1.

Two patients were unable to achieve RVR and had significant viral load (520 and 777 IU/mL) during quantitative HCV RNA estimation at week-4 of the treatment. However, all the patients achieved virological response at the end-of treatment (ETR 100%; $n = 10/10$). None of the patient experienced virological relapse and hence rate of SVR-12 was 100%. There was significant reduction in aspartate aminotransferase ($p = 0.005$) and alanine aminotransferase level ($p = 0.005$) and serum ferritin level ($p = 0.028$) after completion of the antiviral treatment (Table 2).

Adverse events during study mainly consisted of nausea, vomiting (three patients) and anorexia (two patients)

Table 1 Baseline Demographic and Clinical Characteristics of Hepatitis-C Virus Infected Patients with β -Thalassemia Major.

Characteristics	N = 10
Age (years), median (IQR)	13 (10.25–18)
Male, n (%)	10 (100%)
Treatment-naïve, n (%)	10 (100%)
HCV ^a genotype-3, n (%)	10 (100%)
log ₁₀ HCV RNA level, mean $\pm$ SD	5.45 $\pm$ 1.05
Fibroscan score (kPa), mean $\pm$ SD	9.12 $\pm$ 1.91
Total bilirubin (mg/dL), mean $\pm$ SD	50.90 $\pm$ 0.47
Direct bilirubin (mg/dL), mean $\pm$ SD	0.87 $\pm$ 0.49

^aHepatitis C virus.

Table 2 Pre-Treatment and Post-Treatment Laboratory Tests of Patients with β -Thalassemia Major.

Laboratory tests	Pre-treatment	Post-treatment	P-value
Aspartate aminotransferase (U/L), median (interquartile range)	88.00 (60.50–113.25)	37.50 (31.25–57.00)	0.005
Alanine aminotransferase (U/L), median (interquartile range)	77.50 (56.75–110.25)	51 (26.75–72.75)	0.005
Serum ferritin (ng/ml), median (interquartile range)	5207.95 (4069.18–7662.75)	3421.00 (2700.50–5137.50)	0.028

which were managed conservatively. However, none of the patients required discontinuation of treatment or reduction of the dose of antiviral drugs. Moreover, there was no change in blood-transfusion requirement or iron-chelating therapy during study period.

DISCUSSIONS

The chronicity and potentially fatal nature of HCV infection pose a considerable burden on the management of the thalassemia patients. The adopted antiviral treatment approach for chronic HCV infection in thalassemia patients is monotherapy with Pegylated Interferon- α (PegINF- α) since the product monograph of ribavirin does not recommend its use in this cohort (as it leads to haemolytic anaemia).³ The SVR rate with INF therapy varied from 13% to 80%.^{11,12} Recent studies suggest higher SVR with combination therapy of Ribavirin (RBV) and PegINF- α .^{13,14} However, the use of RBV is still a controversial issue in view of increase requirement of blood-transfusion and iron-chelation therapy. Hence, an alternative antiviral treatment regimen needs to be identified. Recently, results of C-EDGE trial, a multicentre phase-III study which assessed safety and efficacy of Elbasvir/Grazoprevir across a spectrum of patients with inherited bleeding disorders (β -thalassemia, sickle cell disease, haemophilia A/B and von Willebrand disease), encourage treatment of HCV infection with DAA in this difficult-to-treat cohort.¹⁵

In India, the prevalence of HCV in thalassemic patients as reported by recent epidemiological studies varies from 18.2% to 25%.^{16–19} Though observational studies demonstrated high SVR rates in real life cohorts of Indian patients with SOF-based treatment, there was no well-established Indian guideline for treatment of HCV with DAA in thalassemic patients.^{6,20} Hence, we carried out this study to evaluate efficacy and safety of SOF-based regimen in this special population. In our study, all the included patients were diagnosed with β -thalassemia major on the basis of haemoglobin electrophoresis, family study or DNA analysis earlier in their life. As it seems unwise to deny them SOF-based treatment due to lack of evidence, the patients (and their legal guardians) were informed all the available antiviral treatment in India, including SOF-based treatment. Final decision to initiate SOF-based treatment was made by patients (or their legal guardians). After their

informed consent, the treatment was initiated with vigilant monitoring. It should be noted that paediatric patients in our study tolerated same regimen as that of adult patients. All the patients also achieved SVR-12. None of the patients required discontinuation of treatment or reduction of the dose. However, interpretation of the results needs consideration of younger thalassemic patients and shorter duration of hepatitis/a lesser amount of impairment of liver that may play important role in treatment outcomes. Moreover, the study results showed significant reduction of aspartate aminotransferase, alanine aminotransferase level and serum ferritin level after completion of treatment.

The peculiarity of this study was that out of 10 patients, seven were paediatric patients. Recently, Balistreri et al. reported safety and efficacy of ledipasvir (90 mg)-SOF (400 mg) for 12 weeks in treating adolescents with HCV infection (genotype 1) without affecting their short-term development (as measured by Tanner pubertal staging).²¹ Moreover, pharmacokinetic studies in 10 patients demonstrated that levels of SOF, GS-331007 (a metabolite of SOF), and ledipasvir in adolescents were within the pre-defined pharmacokinetic equivalence boundaries of 50–200% when compared with adults from Phase 2 and 3 studies. However, to the best of our knowledge, none of the real-life studies demonstrated safety and efficacy of DAA in paediatric patient population. Hence, this study provides an evidence of safety and efficacy of DAA (SOF and DCV) in real-life paediatric population. However, few limitations of the study should be addressed which are as follow: (1) smaller number of patients treated with SOF-based treatment and (2) liver biopsy was not performed and hence the degree of liver siderosis was not known.

In conclusion, the results of the study demonstrated that non-cirrhotic, treatment-naïve β -thalassemia major patients infected with genotype-3 HCV experienced favourable treatment response with combination regimen of SOF and DCV. However, further studies with larger patient populations in randomized controlled trials are needed to build up stronger evidence of safety and efficacy of this treatment approach for HCV in thalassemic patients.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

1. Jafroodi M, Asadi R, Heydarzadeh A, Besharati S. Effect of hepatic iron concentration and viral factors in chronic hepatitis C-infected patients with thalassemia major, treated with interferon and ribavirin. *Int J Gen Med*. 2011;4:529–533.
2. Di Marco V, Capra M, Angelucci E, et al. Management of chronic viral hepatitis in patients with thalassemia: recommendations from an international panel. *Blood*. 2010;116:2875–2883.
3. Angelucci E, Pilo F. Treatment of hepatitis C in patients with thalassemia. *Haematologica*. 2008;93:1121–1123.
4. Di Marco V, Capra M, Gagliardotto F, et al. Liver disease in chelated transfusion-dependent thalassemics: the role of iron overload and chronic hepatitis C. *Haematologica*. 2008;93:1243–1246.
5. Martin S, Schneider B, Heinemann L, et al. Self-monitoring of blood glucose in type 2 diabetes and long-term outcome: an epidemiological cohort study. *Diabetologia*. 2006;49:271–278.
6. Mehta R, Kabrawala M, Nandwani S, et al. Efficacy and safety of sofosbuvir-based therapy for chronic hepatitis C infection in “real-life” cohort. *Indian J Gastroenterol*. 2016;35:459–464.
7. Steinebrunner N, Sprinzl MF, Zimmermann T, et al. Early virological response may predict treatment response in sofosbuvir-based combination therapy of chronic hepatitis C in a multi-center “real-life” cohort. *BMC Gastroenterol*. 2015;15:97.
8. Cho Y, Cho EJ, Lee J-H, Yu SJ, Yoon J-H, Kim YJ. Sofosbuvir-based therapy for patients with chronic hepatitis C: early experience of its efficacy and safety in Korea. *Clin Mol Hepatol*. 2015;21:358–364.
9. Bristogiannis S, Kattamis A, Kyriakopoulou D, Moraki M, Kountouras D, Alexiou N. The effect of hepatitis C—direct-acting antiviral treatment on the hematological profile of thalassemic patients. *Blood*. 2016;128:2471.
10. Biliotti E, Palazzo D, Serani M, et al. Interferon free antiviral treatment of chronic hepatitis C in patients affected by beta-thalassemia major. *Ann Hematol*. 2017;96:1043–1045.
11. Alavian SM, Tabatabaei SV. Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis. *J Viral Hepat*. 2010;17:236–244.
12. Vafiadis I, Trilianos P, Vlachogiannakos J, et al. Efficacy and safety of interferon-based therapy in the treatment of adult thalassemic patients with chronic hepatitis C: a 12 years audit. *Ann Hepatol*. 2013;12:532–538.
13. Seyed Vahid T, Maryam K, Bitra B, et al. Low dose ribavirin for treatment of hepatitis C virus infected thalassemia major patients; new indications for combination therapy. *Hepat Mon*. 2012;2012:372–381.
14. Sood A, Sobti P, Midha V, et al. Efficacy and safety of pegylated IFN alfa 2b alone or in combination with ribavirin in thalassemia major with chronic hepatitis C. *Indian J Gastroenterol*. 2010;29:62–65.
15. Hezode C, Colombo M, Bourliere M, et al. Elbasvir/grazoprevir for patients with hepatitis C virus infection and inherited blood disorders: a phase III study. *Hepatology*. 2017.
16. Manisha S, Sanjeev K, Seema N, Dilip C, Rashmi D. A cross-sectional study on burden of hepatitis C, hepatitis B, HIV and Syphilis in multi-transfused thalassemia major patients reporting to a government hospital of central India. *Indian J Hematol Blood Transfus*. 2015;31:367–373.
17. Jain R, Perkins J, Johnson ST, et al. A prospective study for prevalence and/or development of transfusion-transmitted infections in multiply transfused thalassemia major patients. *Asian J Transfus Sci*. 2012;6:151–154.
18. Makroo RN, Arora JS, Chowdhry M, Bhatia A, Thakur UK, Minimol A. Red cell alloimmunization and infectious marker status (human immunodeficiency virus, hepatitis B virus and hepatitis C virus) in multiply transfused thalassemia patients of North India. *Indian J Pathol Microbiol*. 2013;56:378–383.
19. Prakash A, Aggarwal R. Thalassemia major in adults: short stature, hyperpigmentation, inadequate chelation, and transfusion-transmitted infections are key features. *N Am J Med Sci*. 2012;4:141–144.
20. Sood A, Midha V, Mahajan R, et al. Results of sofosbuvir based combination therapy for chronic hepatitis C cohort of Indian patients in real life clinical practice. *J Gastroenterol Hepatol*. 2016.
21. Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir–sofosbuvir in adolescents 12 to 17 years old with hepatitis C virus genotype 1 infection. *Hepatology*. 2016.