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Safety and efficacy of direct-acting antiviral drugs in the treatment of chronic hepatitis C virus infection in patients with thalassemia: a prospective study

Elsayed Ghoneem[1], Ahmed Saleh[1*], Shahira Aly El-Etreby[1], Metwaly Ibrahim Mortada[2], Mayada A. Ghannam[2], Shaimaa El-Ashwah[3] and Noha Eisa[3]

Abstract

Background: Hepatitis C virus (HCV) infection is a major cause of liver-related morbidity and mortality among thalassemic patients. Direct-acting antiviral agents (DAAs) are highly effective and well-tolerated by chronic HCV patients.

Results: The mean age of our patients was 29 years. Sustained virologic response (SVR) at 12 and 24 weeks was achieved in all patients (100%). The most common side effects were fatigue (18%), anemia (13.63%), and headache (4.5%). There was no statistically significant difference in the hemoglobin level before and after treatment ($p = 0.48$). There was a significant improvement in serum bilirubin and mean ALT levels after treatment compared to baseline data ($p < 0.0005$ each).

Conclusions: DAAs, namely, sofosbuvir plus daclatasvir or sofosbuvir plus ledipasvir, are effective and well-tolerated regimens in thalassemic patients with chronic HCV.

Keywords: Thalassemia, Chronic hepatitis C, Direct-acting antiviral drugs (DAAs), Sustained virologic response (SVR), Post-transfusion hepatitis (PTH)

Background

Viral hepatitis, mainly the hepatitis C virus, is one of the common causes of post-transfusion hepatitis (PTH) in patients who need multiple blood transfusions [1]. Thalassemia is a hereditary disorder characterized by the synthesis of abnormal hemoglobin (genetic deficiency in the synthesis of beta-globin chains), resulting in hemolysis and anemia. Patients with β thalassemia major (BTM) usually require repeated blood transfusion, which keeps them at high-risk of HCV infection [2]. In spite of improvements in the screening of blood products in the last decades to minimize the risk of transmission of blood-borne diseases, viral hepatitis, especially HCV, remains an important problem in patients with β thalassemia [3, 4]. Post-transfusion HCV infection leads to chronic hepatitis with hepatocellular necrosis, fibrosis, and cirrhosis in patients with thalassemia with higher morbidity and mortality [5].

Chronic HCV infection (CHC) treatment in β thalassemia patients was challenging in the interferon (IFN)-based therapy era not only because of its modest efficacy [6–10] but also due to unfavorable safety and tolerability profiles, as it was necessary to be combined with ribavirin (RBV) considering subsequent hemolysis and increased need for blood transfusions, and, thereby, increased risk of iron overload [11].

With the introduction of the new IFN plus RBV free regimens in 2014, the management of all patients with

* Correspondence: drahmedsaleh1981@gmail.com
[1]Department of Internal Medicine, Hepatology & Gastroenterology Unit, Faculty of Medicine, Mansoura University, Mansoura, Egypt
Full list of author information is available at the end of the article

chronic HCV infection, including those with β thalassemia, has dramatically improved. These drugs are direct-acting antivirals (DAAs) that act by targeting specific steps in the HCV life cycle and are used in combinations to treat CHC. In Egypt, depending on the genotype and the drug availability, the available DAAs combinations are the co-formulation of sofosbuvir (SOF) with ledipasvir (LDV) (one tablet of 400/90 mg once daily) and SOF plus daclatasvir (DCV) (in two tablets of 400/60 mg/day once daily). They are nucleotide analog NS5B polymerase inhibitor/NS5A inhibitor. According to guidelines, β thalassemia patients should be treated with IFN- and RBV-free regimens [12].

Different DAAs regimens have been reported to be safe and effective in the treatment of CHC patients in clinical practice [12]. Our thalassemia patients were followed up in a hematology clinic at Oncology Center, Mansoura University (OCMU). Such patients who are also infected with HCV could be a target population for "HCV micro-elimination" on the road toward global HCV elimination in our country.

Methods

Patients

This is a prospective study that included 88 treatment naïve patients with chronic HCV genotype 4 infection and beta-thalassemia major from attendees of Hematology Clinic at Oncology Center, Mansoura University, from January to December 2017. All included patients were transfusion-dependent and were using iron chelation therapy. Only four patients had concomitant hepatitis B virus (HBV) coinfection.

Inclusion criteria for DAAs

Patients of both genders included for DAAs therapy in the current study were diagnosed with Thalassemia major and were on regular transfusion and iron chelation therapy, aged 12 years and above, naïve chronic hepatitis C genotype 4 infection with detectable HCV-RNA by RT-PCR. No additional drugs were used.

Exclusion criteria

Patients were excluded from the study if they were infected with other HCV genotypes, had concomitant HIV infection, or had presence of liver cell failure.

Diagnosis of HCV and genotyping

Chronic HCV infection was diagnosed by positive RT-PCR RNA HCV with or without abnormal liver function tests and the presence of stigmata of chronic liver disease (flapping tremors, ascites, edema lower limb, and hepatic encephalopathy). HCV RNA was quantified by real-time PCR assay (COBAS AmpliPrep/COBAS TaqMan 48, Roche Molecular Diagnostics). The HCV genotype was detected by Versant HCV genotype 2.0 assays (LiPA-Siemens, Erlangen, Germany).

Laboratory assessment

The laboratory tests done included complete blood counts, liver enzymes (ALT, AST), serum bilirubin, serum creatinine, α fetoprotein, and INR. The liver fibrosis stage was assessed by a non-invasive tool known as the FIB-4 score [13].

Treatment protocols

At the Virology unit, Specialized Medical Hospital, Mansoura University, Egypt, all patients were evaluated for anti-HCV treatment. Two DAA regimens were used according to the guidelines of the National Committee for Control of Viral Hepatitis (NCCVH) in Egypt. We treated the patients with the following combinations: SOF(400 mg daily) plus DCV(60 mg daily) for the older age group and LDV(90 mg daily)-SOF in the younger age group (12–18 years) for 12 weeks. Only four patients were coinfected with HBV (diagnosed by the presence of detectable HBV DNA by PCR and all of them were HBeAg positive) and treated using LDV/SOF and lamivudine.

Endpoints of the treatment

The primary endpoint was assessed by the achievement of SVR at 12 weeks and at 24 weeks. The secondary endpoint was assessed by the recording of adverse events, increased transfusion requirements, or stoppage of treatment. All patients were on regular transfusion, and the median packed red blood cell units transfused was a unit per 21 days.

Patients' follow up

Clinical and laboratory data were recorded at baseline and at 4, 8, 12, and 24 weeks of therapy.

Statistical analysis

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 17. Quantitative data were described as means (standard deviations) or medians (interquartile ranges), as appropriate. Comparisons between the different groups were performed using the Wilcoxon rank-sum test for variables that were not normally distributed. Qualitative data were presented as numbers and percentages and compared by using the chi-square test. A P value of less than 0.05 was considered statistically significant.

Results

Demographic and clinicolaboratory data

Table 1 shows the demographic, baseline clinical, and laboratory parameters for a total of 88 thalassemic

Table 1 Demographic, basal clinical and laboratory parameters

Variables	No (%) or median (IQR)
Male gender	44 (50%)
Age (years)	29 (12–36)
Subjects with comorbidities	28 (31.82%)
Hypertension	8 (13.63%)
Osteoporosis	12 (13.63%)
HBV	4 (4.54%)
Drug users	4 (4.54%)
Splenectomy	88 (100%)
Iron chelation agent	
Deferiprone	28 (31.82)
Deferasirox	60 (68.18)
Hemoglobin (g/dl)	8.25 (7.3–9)
Platelet count ($\times 10^9$/L)	543 (430–632)
WBCs ($\times 10^9$/L)	27.3 (18.3–50)
AST (IU/L)	71.50 (47–82.30)
ALT (IU/L)	54.45 (28–74)
S. bilirubin (mg/dl)	2.9 (2.5–4)
Direct bilirubin (mg/dl)	0.6 (0.5–0.98)
Albumin (g/dl)	4 (3.8–4.8)
INR	1.2 (1.1–1.3)
S. creatinine (mg/dl)	0.65 (0.6–0.8)
Ferritin (ng/mL)	2500 (1800–4000)
PCR HCV RNA (IU/ml)	941757 (187771–1400000)
FIB-4 score	0.52 (0.47–0.73)

patients with chronic HCV. The median age of our patients was 29 years and males represented 50% of our study participants. Hypertension was found in 13.63% of cases, osteoporosis in 13.63% of cases, and HBV in four cases. All patients were splenectomized. The median hemoglobin level, platelet count, and white blood cell counts were 8.25 gm/dl, 543 × 10^9/L, and 27.3 × 10^9/L respectively. The median AST, ALT, and serum bilirubin levels were 71.5 IU/L, 54,45 IU/L, and 2.9 mg/dl respectively. Serum ferritin levels were elevated with a median level of 2500 ng/ml. The median PCR for HCV RNA was 941757 IU/ml, with a median FIB-4 score of 0.52.

Efficacy of treatment

All patients were treatment naïve. Overall, 64 (72.72%) patients were treated with a SOF plus DCV, and 24 (27.27%) patients received SOF plus LDV for 12 weeks. All patients achieved SVR at 12 weeks and 24 weeks. There was a significant improvement in the mean ALT values after treatment compared to baseline (42.45 ± 18.56 IU/L vs 57.29 ± 35.07 IU/L, $p < 0.0005$, Fig. 1). Also, there was a statistically significant decrease in serum bilirubin level after treatment ($p < 0.0005$, Fig. 2). There was no statistically significant difference in the hemoglobin level (Fig. 3), platelet count, and WBCs count before and after DAAs (the p values were 0.613, 0.092, and 0.284, respectively) (Table 2). Twelve patients reported increased blood transfusion requirements, although no significant difference was noticed between the mean HB level before and after DAAs.

Safety of the treatment

No major side effects were reported and no patients discontinued the treatment. Only one case required treatment discontinuation (median time of 2 weeks) due to acute kidney injury after the prolonged use of NSAIDs

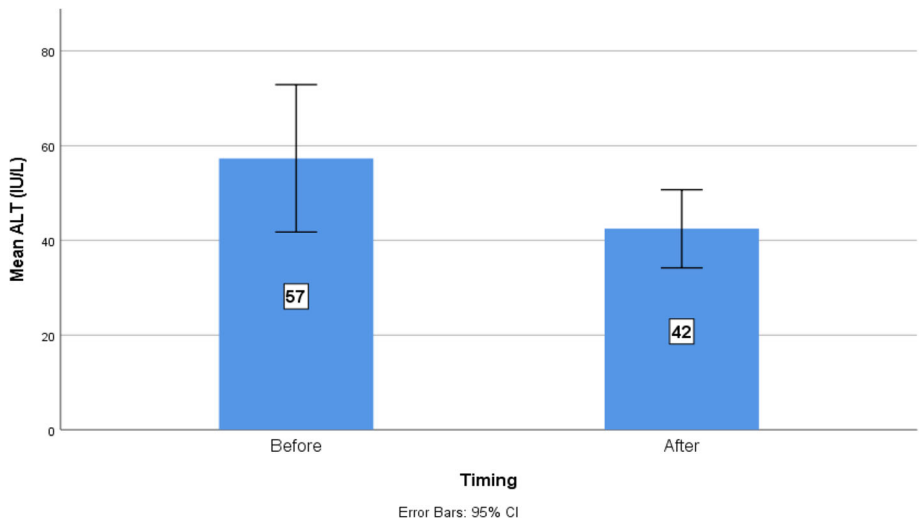

Fig. 1 ALT before and after treatment

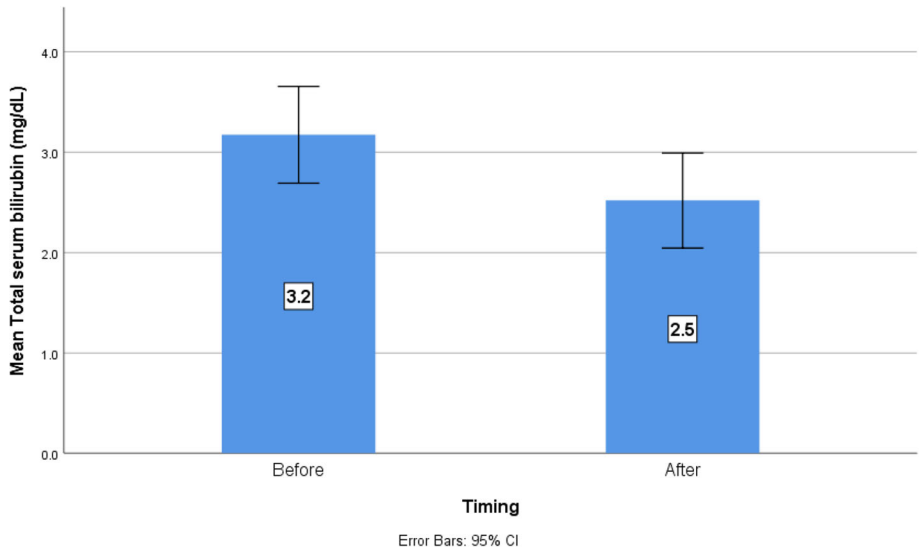

Fig. 2 Serum level of bilirubin before and after treatment

and resumed DAAs after the decline of creatinine to the normal level. Twenty (22.72%) patients complained of mild symptoms. The most common side effects were fatigue (18%), anemia (13.63%), requiring blood transfusion (12 patients) in patients receiving SOF plus DCV, and, lastly, headache (4.5%). These side effects were more frequent among patients receiving SOF plus DCV, than in patients receiving SOF plus LDV; however, this difference in frequency was not statistically significant (60% vs. 40%, $p = 0.58$).

Discussion

HCV infection is considered a major clinical burden in β thalassemia patients. The prevalence of HCV is much higher among patients with beta-thalassemia, as these patients constitute a 4 high-risk group. A systematic review based on the literature database showed that the anti-HCV antibody among β thalassemia patients has been estimated at 18%, 45%, 63%, and 69% in Iran, Pakistan, Saudi Arabia, and Egypt, respectively [14]. Approximately 70–80% of those patients will progress to CHC and up to 20% will go on to cirrhosis [15]. It is also known that HCV infection is a risk factor for HCC, which has been considered as the second common cause of mortality in this population [16].

Herein, our study provides further proof that oral DAAs are highly effective and tolerable by β thalassemia patients with CHC. All enrolled patients achieved SVR

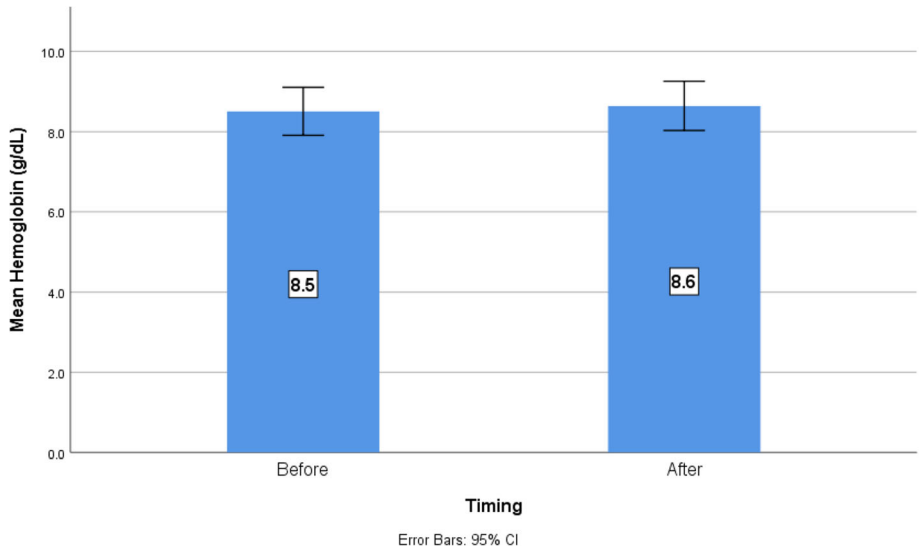

Fig. 3 Hemoglobin level before and after treatment

Table 2 Laboratory parameters before and after treatment with DAAs

Parameter	Before	After	Statistic	*P* value
ALT(IU/ml)	57.29 ± 35.07	42.4545 ± 18.56	3.569	0.0005
S. bilirubin (mg/dL)	3.17 ± 1.08	2.51 ± 1.06	4.800	0.0005
Hemoglobin (g/dL)	8.5 ± 1.34	8.64 ± 1.38	− 0.513	0.613
Platelets count (× 10^9/L)	513.18 ± 160.47	460.14 ± 186.81	1.764	0.092
WBCs (×10^9/L)	27.30 (18.27–51)	20.50 (12.15–49)	− 1.072	0.284

Data presented as mean ± SD except WBCs presented as median (IQR). For WBCs, data were not normally distributed (Shapiro test, $p < 0.05$) with the presence of significant outliers. Accordingly, Wilcoxon test was conducted. Paired samples t test was used for other parameters as the data were normally distributed

at 12 weeks and at 24 weeks. Compared to the Italian cohort [17] and the Greek cohort [18], SVR was achieved in most of the patients (98% and 90%, respectively). Both studies included 57.1% vs. 78.7% and previously treated patients 42.9% vs. 75%. The achievement of 100% SVR in our study could be explained by the fact that all enrolled patients were treatment naïve and had no cirrhosis as the median FIB-4 score was 0.52. However, those patients should be monitored for the possibility of reinfection.

Hezode et al. [19] published a trial using a fixed combination of elbasvir and grazoprevir in patients with congenital blood disorders and CHC, including β thalassemic patients. Forty β thalassemia major patients received treatment for 12 weeks, and SVR was achieved in 97.6% of them. This study showed that treatment was well-tolerated by the patients, and hemoglobin levels were not affected by treatment. The most frequently reported side effects in this study were, e.g., headache, fatigue, nausea, and asthenia. However, this combination is not currently available in Egypt.

Also, in a case series of four β thalassemia patients with CHC associated with advanced hepatic fibrosis, treated with the LDV/SOF combination for 12 weeks, all patients achieved SVR with accepted drug safety and tolerability. The only reported adverse events were mild asthenia and headache. There were no changes in chelation therapy or transfusion requirements during the treatment period. Similar results were presented by Mangia et al. [20, 21].

In the present study, there were no major adverse events, and no discontinuation of treatment was reported. Only one case required temporary treatment discontinuation due to acute kidney injury after the prolonged use of NSAIDs then resumed DAAs after the decline of serum creatinine to the normal value. Mild symptoms occurred in approximately 22.72% of the patients. The most common side effects were fatigue (18%), anemia (13.63%), and headache (4.5%). This is in accordance with the published data from certain clinical trials [18, 22]. These side effects were more common among patients receiving SOF plus DCV than in patients receiving SOF plus LDV; however, this difference in the rates of occurrence of side effects was not statistically significant ($p = 0.58$). Also, no drug-drug interactions were observed.

There was a significant improvement of mean ALT values and a significant decrease in serum bilirubin after treatment. On the other hand, no statistically significant difference in the hemoglobin level, platelet count, and WBCs count were found before and after DAAs. Only 12 patients had increased blood transfusion requirements, despite a non-significant difference being noticed between the mean HB level before and after DAAs. The dose and type of iron-chelating therapy did not require any modifications during the treatment course.

A high hepatic iron concentration was proposed as a negative predictor of response to DAAs in different ethnic populations. There was no consensus on whether iron accumulation in the sinusoidal cells or hepatocytes and portal track macrophages was more significant for poor response to treatment [23].

Assessment of hepatic iron concentration was limited and mainly based on serum ferritin levels and non-invasive techniques without liver histology and the data of post-treatment assessment of hepatic iron overload were not obtainable during the study. So, we need further studies with larger samples and newer DAA combinations.

Conclusion

Direct-acting antiviral drugs (sofosbuvir plus daclatasvir or sofosbuvir plus ledipasvir) are safe, effective, and well-tolerated regimens for thalassemic patients with chronic HCV.

Abbreviations

HCV: Hepatitis C virus; DAAs: Direct-acting antivirals agents; SVR: Sustained virologic response; PTH: Post-transfusion hepatitis; BTM: β thalassemia major; CHC: Chronic HCV infection; IFN: Interferon; RBV: Ribavirin; SOF: Sofosbuvir; LDV: Ledipasvir; DCV: Daclatasvir; OCMU: Oncology Center, Mansoura University; HBV: Hepatitis B virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; NCCVH: National Committee for Control of Viral Hepatitis; HB: Haemogloin

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Authors' contributions
The protocol of the study, study design, methodology, follow-up of the patients, collection of the data, data analysis, and writing—original draft preparation: SEA, NE, and EG. Lab investigation: MM and MG. Writing—review and editing: EG. Supervision: SEE and AS. All authors have read and approved the manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article [and its supplementary information files] and readily available for sharing.

Declarations

Ethics and approval consent to participate
The study has been approved by the ethics committee of our university (Mansoura Faculty of Medicine, Mansoura University, Institutional Review Board Code No R/17.12.71) and has been performed following the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed written consents approved by ethical committee of Mansoura Faculty of Medicine were obtained from all individual participants or their legal guardians if under 16 years.

Consent for publication
NA

Competing interests
The authors declare that they have no conflict of interest.

Author details
[1]Department of Internal Medicine, Hepatology & Gastroenterology Unit, Faculty of Medicine, Mansoura University, Mansoura, Egypt. [2]Department of Clinical Pathology, Hematology Unit, Faculty of Medicine, Mansoura University, Mansoura, Egypt. [3]Department of Clinical Hematology, Oncology Center Mansoura University (OCMU), Faculty of Medicine, Mansoura University, Mansoura, Egypt.

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