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

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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
chronic HCV infection, including those with β thalas-
semia, has dramatically improved. These drugs are
direct-acting antivirals (DAAs) that act by targeting spe-
cific steps in the HCV life cycle and are used in combi-
nations 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 Uni-
versity, 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 chela-
tion 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 in-
fected 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 dis-
ease (flapping tremors, ascites, edema lower limb, and
hepatic encephalopathy). HCV RNA was quantified by
real-time PCR assay (COBAS Amplicor/COBAS Taq-
Man 48, Roche Molecular Diagnostics). The HCV
genotype was detected by Versant HCV genotype 2.0 as-
says (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 fi-
brosis stage was assessed by a non-invasive tool known
as the FIB-4 score [13].

Treatment protocols
At the Virology unit, Specialized Medical Hospital, Man-
soura University, Egypt, all patients were evaluated for
anti-HCV treatment. Two DAA regimens were used ac-
cording 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 end-
point was assessed by the recording of adverse events,
increased transfusion requirements, or stoppage of treat-
ment. 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 de-
viations) or medians (interquartile ranges), as appropri-
ate. Comparisons between the different groups were
performed using the Wilcoxon rank-sum test for vari-
ables that were not normally distributed. Qualitative data
were presented as numbers and percentages and com-
pared 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 la-
bratory parameters for a total of 88 thalassemic
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.

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 (×10^9/L)       | 543 (430–632)          |
| WBCs (× 10^9/L)                | 27.3 (18.3–50)         |
| ALT (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)       |

![Fig. 1 ALT before and after treatment](image)
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 \( \beta \) thalassemia patients. The prevalence of HCV is much higher among patients with beta-thalassemia, as these patients constitute a high-risk group. A systematic review based on the literature database showed that the anti-HCV antibody among \( \beta \) 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 \( \beta \) thalassemia patients with CHC. All enrolled patients achieved SVR.
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: Haemoglobin

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**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   |
| Platelet count (x 10^9/L)  | 513.18 ± 160.47         | 460.14 ± 186.81        | 1.764     | 0.092   |
| WBCs (x10^3/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.
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: 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, Mansoura, Egypt). 2Department of Clinical Pathology, Hematology Unit, Faculty of Medicine, Mansoura University, Mansoura, Egypt. 3Department of Clinical Hematology, Oncology Center Mansoura University (OCMU), Faculty of Medicine, Mansoura University, Mansoura, Egypt.

Consent for publication
NA

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

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