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Safety and Efficacy of Direct-Acting Antivirals in Transfusion-Dependent Thalassemic Patients with Chronic Hepatitis C

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Abstract

Background: Hepatitis C virus (HCV) infection is a major cause of liver-related morbidity and mortality among thalassemic patients. New treatments based on direct-acting antivirals (DAAs) are highly effective and well-tolerated by patients; nonetheless, they have not been studied in thalassemic populations. In this study, we evaluated the safety and efficacy of these treatments in a cohort of Sardinian thalassemic patients with chronic HCV infection.

Methods: We consecutively recruited thalassemic patients with HCV infection, who were eligible for DAA therapy at 3 liver units. Different drug combinations, depending on HCV genotype and hepatic disease severity, were used according to the current guidelines. Sustained virological response was assessed at 12 weeks posttreatment. Data regarding the side effects and transfusion requirements were also collected.

Results: We recruited 49 patients, including 29 males (59.2%), with the mean age of 43 years (genotype 1, 55.1%). Twenty-one (42.9%) patients had a history of interferon-based treatment. Cirrhosis was detected in 28 (57.1%) patients; only 1 patient had ascites and hypoalbuminemia (Child-Pugh B7). On the other hand, 35 (71.4%) patients received a sofosbuvir-based regimen. Ribavirin treatment was reported in 26 (53.1%) cases. All the patients were followed-up for at least 12 weeks after therapy, and sustained virological response was observed in 98% of the patients. No treatment discontinuation was required due to adverse events. The most common side effects included fatigue (24.5%), headache (10.2%), and anaemia (77%), requiring further blood transfusion in patients receiving ribavirin.

Conclusions: This prospective study showed that DAAs are safe and effective agents in thalassemic patients with advanced liver fibrosis, regardless of previous antiviral treatment responses.

Keywords: Thalassemia, HCV, DAAs, Blood Transfusion

1. Background

HCV infection is a major clinical problem in transfusion-dependent thalassemic patients (1). Along with iron overload, it represents a main risk factor for the development of liver fibrosis and eventually cirrhosis in this population (2). Various studies have shown a faster progression to severe liver fibrosis in patients with concomitant HCV infection and high liver iron concentrations. The prevalence of cirrhosis in these patients ranges from 10% to 20% (3-5).

Although the overall survival of thalassemic patients has recently increased due to improvements in iron chelation therapy and the subsequent reduction in cardiac complications, liver-related mortality and morbidity rates have risen because of liver failure and development of hepatocellular carcinoma (6). Therefore, eradication of hepatitis C virus (HCV) infection has become a priority in these patients.

Until recently, the only available treatment for HCV infection was the combination of pegylated interferon-α (PEG-IFN-α) and ribavirin (RBV), which showed modest efficacy in thalassemic populations (7-11). However, its use

was limited by poor tolerance, several contraindications, and concerns about RBV-induced haemolysis and the subsequent increase in transfusion needs (12).

More recently, IFN-free regimens, based on direct-acting antivirals (DAAs), have been developed, showing greater efficacy and tolerance in patients with chronic HCV infection. According to international guidelines, thalassemic patients should be treated with these new regimens, preferably those without RBV (13). However, only few thalassemic patients have been examined in clinical trials, and very limited data exist regarding real-life experiences (14-17). A recent study by Sinakos et al. described the outcomes of 61 thalassemic patients with advanced liver fibrosis, who received different IFN-free regimens in Greece. They reported a sustained virological response (SVR) rate of 90% with good tolerance and no major adverse events (18).

With this background in mind, in this prospective study, we aimed to investigate the safety and efficacy of DAA-based regimens in a cohort of thalassemic patients, affected by chronic HCV infection and advanced liver fibrosis.

2. Methods

We prospectively recruited all consecutive patients with chronic HCV infection and beta-thalassemia major (BTM), who underwent antiviral therapy with DAAs plus RBV between March 2015 and December 2016 at 3 liver units in Sardinia, Italy (Azienda Ospedaliero Universitaria di Cagliari, Azienda Ospedaliero Universitaria di Sassari, and Ospedale San Francesco di Nuoro).

Chronic HCV infection was defined as the presence of HCV RNA and abnormal alanine aminotransferase (ALT) level for more than 6 months. The diagnosis of BTM was based on the classic peripheral blood count and haemoglobin electrophoresis. All the patients were transfusion-dependent and received iron chelation therapy. On the other hand, subjects with concomitant hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV) coinfection were excluded. Relapsers and nonresponders to prior antiviral therapy with IFN and RBV were included in this study.

Different DAA-based regimens were used according to the European Association for the Study of the Liver (EASL) and Associazione Italiana Studio Fegato (AISF) guidelines, depending on HCV genotype, hepatic disease severity, and drug availability during the study. Genotype-1 patients were treated with the following combinations: sofosbuvir plus simeprevir, sofosbuvir plus daclatasvir, sofosbuvir plus ledipasvir, and ombitasvir-paritaprevir boosted with ritonavir plus dasabuvir. Genotype-2 and -3 patients received sofosbuvir plus RBV or sofosbuvir plus daclatasvir. Moreover, genotype-4 patients were treated with sofosbuvir plus simeprevir, sofosbuvir plus daclatasvir, sofosbuvir plus ledipasvir, and ombitasvir-paritaprevir boosted with ritonavir.

The treatment duration ranged from 12 to 24 weeks. RBV could be added at the physician's discretion in "difficult-to-treat" genotype-1, -3, and -4 patients, such as cirrhotic patients and those with a history of antiviral treatment. The choice of treatment was also affected by the presence of potential drug-drug interactions and daily pill burden. Clinical and laboratory data were collected at baseline, 2, 4, 8, 12, and 24 weeks of therapy (if applicable), and 1, 3, and 6 months after the completion of therapy. The side effects and blood transfusion requirements before, during, and following the antiviral treatment were monitored at each clinical visit.

The HCV genotype was detected by Versant HCV genotype 2.0 assay (LiPA-Siemens, Erlangen, Germany). HCV RNA was quantified by real-time polymerase chain reaction (PCR) assay (COBAS AmpliPrep/COBAS TaqMan 48, Roche Molecular Diagnostics). Moreover, the liver fibrosis stage was assessed via liver stiffness measurement, using transient elastography (FibroScan®, Echosens, Paris, France) or liver histology if available.

The diagnosis of cirrhosis was based on either typical laboratory and ultrasound findings or liver stiffness value equal to or greater than 13 kPa (19). In addition, iron overload was assessed by the measurement of serum ferritin level, as well as cardiac and hepatic magnetic resonance imaging (MRI) when available. Finally, SVR was defined as undetectable serum HCV RNA at 12 weeks following therapy discontinuation.

The present study was performed in accordance with the Declaration of Helsinki and was approved by the Local Ethics Committee (Independent ethics committee of Azienda Ospedaliero Universitaria di Cagliari, Italy). All the participants gave an informed consent for the use of data on the condition that their information remained anonymous. Drugs were provided by the National Health Service (NHS) according to the Italian principles.

2.1. Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median (range) when applicable. Comparisons between the groups were performed using paired t test for parametric variables or Wilcoxon rank-sum test for nonparametric variables. Categorical variables are expressed as number and percentage and compared by Chi-square test. P value below 0.05 was considered statistically significant.

3. Results

3.1. Study Population

A total of 49 patients were enrolled in the study (Table 1). All the subjects were transfusion-dependent, and the median transfused, packed red blood cell (PRBC) count was 2 units per month. Most of the patients were infected by HCV genotype 1b (42.9%) and had liver cirrhosis (57.1%), diagnosed via liver stiffness measurement (n, 24), ultrasound examination (n, 3), or liver histology (n, 1). All cirrhotic patients had a well-compensated disease except one patient with diuretic-controlled ascites and hypoalbuminemia (Child-Pugh B7).

A total of 21 (42.9%) patients had a history of antiviral treatment, receiving IFN with or without RBV (n, 11) or PEG-IFN plus RBV (n, 10); eight patients were relapsers, while 13 were nonresponders. Comorbidities were identified in 29 (59.2%) patients, 17 of whom had cardiovascular diseases, such as hypertension (n, 4), atrial fibrillation (n, 6), and heart failure (n, 7). Also, 10 (20.4%) patients had diabetes, while 9 (18.4%) patients presented with hypothyroidism, requiring hormonal replacement therapy. The MRI data on hepatic and cardiac iron accumulation were only available in 20 (40.8%) patients; IFN-free regimens are illustrated in Table 2. Overall, 35 (71.4%) patients were treated with a sofosbuvir-based antiviral treatment, and 26 (53.1%) patients received RBV.

3.2. Treatment Response

Overall, 28 (57.1%) and 44 (89.7%) patients showed undetectable HCV RNA after 2 and 4 weeks of therapy, respectively. All the patients had an undetectable viral load at week 8 of treatment. All the patients completed the treatment with undetectable HCV RNA and were followed-up for at least 12 weeks posttreatment. Overall, 48 (98%) patients achieved SVR. Only 1 case of relapse was reported at 1 month posttreatment. The patient was a cirrhotic man with HCV genotype 4, who was previously unresponsive to IFN + RBV regimen, but was treated with sofosbuvir and simeprevir. He was successfully treated with sofosbuvir and ledipasvir a few months later.

3.3. Safety

No major adverse events were reported, and none of the patients discontinued treatment due to side effects. Nineteen (38.8%) patients complained of mild symptoms (Table 2), which were more frequent among those receiving RBV, compared to DAAs alone (57.7% vs. 17.4%; P = 0.004). No significant difference was observed in the frequency of the side effects of RBV-free regimens between cirrhotic and noncirrhotic patients.

Table 1. The Patients' Baseline Characteristics (N, 49)[a]

Variables	Value
Male sex, No. (%)	29 (59.2)
Age, years	43 (5)
Cirrhosis, No. (%)	28 (57.1)
Child-Pugh score, No. (%)	
A5	21 (42.9)
A6	6 (12.2)
B7	1 (2.0)
Liver stiffness, kPa	13.6 (10 - 33.3)
HCV genotype, No. (%)	
1a	6 (12.2)
1b	21 (42.9)
2	9 (18.4)
3	5 (10.2)
4	8 (16.3)
History of antiviral treatment	21 (42.9)
IFN	5 (10.2)
IFN + RBV	6 (12.2)
PEG-IFN + RBV	10 (20.4)
Splenectomy	20 (40.8)
Subjects with comorbidities, No. (%)	29 (59.2)
Cardiovascular complications	17 (34.7)
Diabetes	10 (20.4)
Hypothiroidism	9 (18.4)
Hepatic T2*, ms	14.8 (0.9 - 34)
Cardiac T2*, ms	28.4 (8.8 - 48.3)
Iron chelation agent, No. (%)	
Deferoxamine	28 (57.1)
Deferiprone	7 (14.3)
Deferasirox	9 (18.4)
Deferoxamine + deferiprone	3 (6.1)
Deferasirox + deferiprone	2 (4.1)
Body mass index, kg/m^2	22.4 (17 - 27.5)
Haemoglobin, g/dL	10.8 (8 - 13.2)
Platelet count, $\times 10^9$/L	242 (99 - 895)
AST, IU/L	57 (18 - 150)
ALT, IU/L	81 (19 - 268)
Bilirubin, mg/dL	1.91 (0.5 - 6)
Albumin, g/dL	4.1 (3 - 4.9)
INR	1.15 (0.9 - 3.9)
Ferritin, ng/mL	926 (78 - 6677)
HCV viral load, IU/mL	389,000 (2460 - 23,780,000)

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; IFN, Interferon; INR, International Normalized Ratio; PEG-IFN, Pegylated-Interferon; RBV, Ribavirin.
[a] Quantitative values are presented as mean and standard deviation or median and range when applicable.

In patients receiving RBV (n, 26), anaemia was the most common adverse event, as reported in 20 (77%) patients. A significant increase in the median number of transfused PRBCs per month was reported (600 mL/month at baseline vs. 2400 mL/month during treatment; P < 0.001). The RBV dose was also reduced in 7 out of 26 patients. Transfusion

Table 2. DAA Regimens According to HCV Genotype and Fibrosis Stage

Fibrosis Stage	HCV Genotype	Total Number of Patients	Antiviral Regimens	Duration, Weeks	SVR, %
F3	1a	1	SOF-DCV	12	100
	1b	10	SOF-SIM (n, 3)	12	100
			SOF-DCV (n, 1)		
			OBV-PTV-r + DSV (n, 4)		
			SOF-LED (n, 2)		
	2	5	SOF + RBV	12	100
	3	1	SOF + RBV	24	100
	4	4	SOF-LED (n, 1)	12	100
			SOF-LED + RBV (n, 1)		
			OBV-PTV-r + RBV (n, 2)		
F4	1a	5	SOF-LED (n, 3)	24	100
			SOF-LED + RBV (n, 2)		
	1b	11	SOF-SIM + RBV (n, 2)	12	100
			OBV-PTV-r + DSV (n, 2)	12	
			OBV-PTV-r + DSV + RBV (n, 5)	12	
			SOF-DCV (n, 1)	24	
			SOF-LED + RBV (n, 1)	24	
	2	4	SOF-DCV (n, 1)	12	100
			SOF + RBV (n, 1)	16	
			SOF + RBV (n, 2)	24	
	3	4	SOF-DCV (n, 1)	24	100
			SOF-DCV + RBV (n, 3)	24	
	4	4	SOF-SIM (n, 2)	12	50
			SOF-DCV (n, 1)	24	100
			OBV-PTV-r + RBV (n, 1)	24	100

Abbreviations: DCV, Daclatasvir; DSV, Dasabuvir; LED, Ledipasvir; OBV-PTV/r, Ombitasvir-Paritaprevir-Ritonavir; RBV, Ribavirin; SIM, Simeprevir; SOF, Sofosbuvir.

requirements returned to the baseline within 1 month after treatment. Two patients reported an increase in blood transfusion requirements, although they did not receive RBV. Iron chelating therapy did not require any modifications during treatment, and no significant drug-drug interactions were observed.

4. Discussion

HCV infection represents a major clinical issue in patients with transfusion-dependent thalassemia. The prevalence of anti-HCV antibody in this population ranges from 4.4% to 85.2% according to different studies, with the highest rates reported in Italy (3). About 70% - 80% of infected patients develop chronic hepatitis, and up to 20% progress to cirrhosis (20). Moreover, HCV infection is a well-known risk factor for the development of hepatocellular carcinoma, which has become the second most common cause of mortality in this population (6).

Until recently, the combination of PEG-IFN-α and RBV was the only available treatment for HCV infection, with variable SVR rates of 25% - 72% (7-11). However, its application was limited by poor tolerance, several contraindications, and concerns about RBV-induced haemolysis and the subsequent increase in transfusion needs and iron overload (12). Recently, introduction of DAAs has dramatically changed HCV treatment due to its high efficacy (SVR > 90%) and superior safety profile, compared to IFN-based

Table 3. The Frequency of Side Effects During Treatment[a]

Varibles	Total Number of Patients (N, 49)	No RBV (N, 23)	RBV (N, 26)	P Value
Anaemia	22 (45)	2 (8.7)	20 (77)	< 0.001
Fatigue	12 (24.5)	3 (13.0)	9 (34.6)	0.08
Headache	5 (10.2)	2 (8.7)	3 (11.5)	0.74
Nausea	2 (4.1)	1 (4.3)	1 (3.8)	0.93
Oral aphtha	2 (4.1)	0	2 (7.7)	0.17
Rash	1 (2.0)	0	1 (3.8)	0.34
Pruritus	1 (2.0)	1 (4.3)	0	0.28
Sleepiness	1 (2.0)	0	1 (3.8)	0.34
Irritability	1 (2.0)	0	2 (7.7)	0.17

Abbreviation: RBV, Ribavirin.
[a]Values are expressed as No. (%).

therapy. Although limited data exist on the use of DAAs in this population, thalassemic patients should receive these new regimens according to the current guidelines (13).

Hezode et al. published the only clinical trial on thalassemic patients (14). They evaluated the safety and efficacy of a fixed combination of elbasvir and grazoprevir in patients with chronic HCV and congenital blood disorders, including BTM. Forty-one thalassemic patients were treated for 12 weeks, and SVR was achieved in 97.6% of cases. In this study, treatment was well-tolerated by the patients, and haemoglobin levels did not change during treatment. Interestingly, the most frequent side effects (e.g., headache, fatigue, nausea, and asthenia) were similar to those observed in our population, although none of our patients received the coformulation of elbasvir and grazoprevir, as it was not available during the study.

A case-series of 4 thalassemic patients with HCV infection and advanced liver fibrosis, treated with ledipasvir and sofosbuvir for 12 weeks, has been also reported (15). All patients achieved SVR and tolerated therapy. Mild asthenia and headache were again the only reported adverse events. No changes in chelation therapy or transfusion requirements were necessary during treatment. Similar results have been presented by Mangia et al. in a report from an Italian multicenter study (16).

The safety and efficacy of DAAs were also assessed in a prospective Indian study, including 29 thalassemic patients treated with 2 generic sofosbuvir-based regimens. SVR was reported in all patients, with no treatment discontinuation due to side effects (17). Finally, a recent study by Sinakos et al. reported the outcomes of a larger cohort of 61 thalassemic patients with chronic HCV infection and advanced liver fibrosis, receiving different IFN-free regimens in Greece (18). Overall, the SVR rate was 90%, and no major adverse events or drug-drug interactions were observed. Six patients relapsed, and no specific factors associated with treatment failure could be identified.

The present study provides further evidence that all-oral anti-HCV regimens are highly effective and well-tolerated by transfusion-dependent thalassemic patients with advanced liver fibrosis. Compared to the Greek cohort, SVR was achieved in a greater number of patients (98% vs. 90%), with only 1 case of relapse after treatment discontinuation. This could be due to the lower number of patients with unfavourable profiles in our population compared to the Greek cohort such as cirrhotic individuals (57.1% vs. 78.7%) and previously treated patients (42.9% vs. 75%).

Moreover, use of suboptimal treatments, such as sofosbuvir plus simeprevir for genotype 1 - 4 patients and sofosbuvir plus RBV for genotype 1 - 3 patients, was limited to 8 out of 49 (16%) patients, compared to 21 out of 61 (34%) patients in the Greek cohort. In our population, the proportion of patients receiving RBV was almost twice as high as that reported by Sinakos et al. (53% vs. 26%). This could be explained by the higher frequency of patients with HCV genotype 2, whose only therapeutic option has been sofosbuvir + RBV for a long time (16.3% vs. 3%). Moreover, the extensive use of triple DAA combination plus RBV for genotype 1b patients and ombitasvir/paritaprevir/ritonavir plus RBV for genotype 4 patients, which was less frequent in the Greek study, might be effective.

Anaemia occurred in about 77% of patients receiving RBV, with doubled transfusion requirements during treatment and no changes in chelation therapy. Two more patients, who did not receive RBV, reported an increase in blood transfusion, which could be related to the intensive monitoring protocol during antiviral treatment. Treat-

ment was well-tolerated by all the patients, and no discontinuation occurred due to the adverse events.

Side effects, such as fatigue and headache, were reported in line with the published data from clinical trials (13). This favourable safety profile in the thalassemic population is very important, as these patients have been traditionally considered as difficult-to-treat due to several comorbidities. Moreover, as previously reported by Sinakos et al., no significant drug-drug interactions were observed with iron chelating agents.

The present study had some limitations. First, data on liver iron concentration were limited and mainly based on serum ferritin levels and noninvasive techniques instead of liver histology. Second, no data regarding the posttreatment evaluation of iron overload were available during the study. Third, liver stiffness measurements via transient elastography were only performed at baseline, and no information was collected about changes after HCV eradication.

In conclusion, DAA-based regimens seem to be highly effective and well-tolerated in patients with BTM and advanced liver fibrosis. The present findings support the use of these agents in thalassemic populations, although further studies with larger cohorts and newer DAA combinations are needed.

Footnotes

Authors' Contribution: Study conception and design, Simona Onali, Cinzia Balestrieri, Francesco Arcadu, Ivana Maida, and Luchino Chessa; acquisition of data, Simona Onali, Francesco Enrico Enrico Urru, Davide Porcu, Giacomo Flore, Elena Dore, Caterina Satta, Pier Paolo Bitti, Maria Grazia Sanna, Loredana Serusi, Michele Casale, Maria Conti, Martina Loi, Maria Cristina Pasetto, Ivana Maida, Francesco Arcadu, and Luchino Chessa; analysis and interpretation of data, Simona Onali, Cinzia Balestrieri, Francesco Arcadu, Ivana Maida, and Luchino Chessa; drafting of manuscript, Simona Onali, Francesco Cinzia Cinzia Balestrieri, Francesco Arcadu, Ivana Maida, and Luchino Chessa; and critical revision of manuscript, all authors.

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References

1. Wonke B, Hoffbrand AV, Brown D, Dusheiko G. Antibody to hepatitis C virus in multiply transfused patients with thalassaemia major. *J Clin Pathol*. 1990;**43**(8):638–40. [PubMed: 2119395].
2. Angelucci E, Muretto P, Nicolucci A, Baronciani D, Erer B, Gaziev J, et al. Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. *Blood*. 2002;**100**(1):17–21. [PubMed: 12070002].
3. Di Marco V, Capra M, Angelucci E, Borgna-Pignatti C, Telfer P, Harmatz P, et al. Management of chronic viral hepatitis in patients with thalassemia: recommendations from an international panel. *Blood*. 2010;**116**(16):2875–83. doi: 10.1182/blood-2009-11-248724. [PubMed: 20551378].
4. Di Marco V, Capra M, Gagliardotto F, Borsellino Z, Cabibi D, Barbaria F, et al. Liver disease in chelated transfusion-dependent thalassemics: the role of iron overload and chronic hepatitis C. *Haematologica*. 2008;**93**(8):1243–6. doi: 10.3324/haematol.12554. [PubMed: 18556410].
5. Prati D, Maggioni M, Milani S, Cerino M, Cianciulli P, Coggi G, et al. Clinical and histological characterization of liver disease in patients with transfusion-dependent beta-thalassemia. A multicenter study of 117 cases. *Haematologica*. 2004;**89**(10):1179–86. [PubMed: 15477201].
6. Voskaridou E, Ladis V, Kattamis A, Hassapopoulou E, Economou M, Kourakli A, et al. A national registry of haemoglobinopathies in Greece: deducted demographics, trends in mortality and affected births. *Ann Hematol*. 2012;**91**(9):1451–8. doi: 10.1007/s00277-012-1465-7. [PubMed: 22526366].
7. Casu S, Balestrieri C, Figorilli F, Onali S, Serra G, Chessa L, et al. P1155 safety and efficacy of PEG IFnA 2a and ribavirin for treatment of hepatitis C in sardinian adult patients with thalassemia major, a single centre real life experience. *J Hepat*. 2014;**60**(1):468. doi: 10.1016/s0168-8278(14)61315-5.
8. Paschos P, Vlachaki E, Pasvanti C, Sinakos E, Kalpaka A, Klonizakis P, et al. Safety and efficacy of combination therapy with pegylated interferon alpha-2a and ribavirin in treating patients with chronic hepatitis C and beta-thalassaemia major: a Greek single-center experience. *Acta Haematol*. 2011;**126**(4):231–3. doi: 10.1159/000330516. [PubMed: 21934299].
9. Harmatz P, Jonas MM, Kwiatkowski JL, Wright EC, Fischer R, Vichinsky E, et al. Safety and efficacy of pegylated interferon alpha 2a and ribavirin for the treatment of hepatitis C in patients with thalassemia. *Haematologica*. 2008;**93**(8):1247–51. doi: 10.3324/haematol.12352. [PubMed: 18556414].
10. Inati A, Taher A, Ghorra S, Koussa S, Taha M, Aoun E, et al. Efficacy and tolerability of peginterferon alpha-2a with or without ribavirin in thalassaemia major patients with chronic hepatitis C virus infection. *Br J Haematol*. 2005;**130**(4):644–6. doi: 10.1111/j.1365-2141.2005.05645.x. [PubMed: 16098081].
11. Kamal SM, Fouly AH, Mohamed MK, Hochnikos BW, Lamont FT, Gohary IS, et al. 585 Peginterferon alpha 2b therapy with and without ribavirin in patients with thalassemia, a randomized study. *J Hepatol*. 2006;**44**:217. doi: 10.1016/s0168-8278(06)80585-4.
12. Alavian SM, Tabatabaei SV. Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis. *J Viral Hepat*. 2010;**17**(4):236–44. doi: 10.1111/j.1365-2893.2009.01170.x. [PubMed: 19638104].
13. European Association for the Study of the Liver. Electronic address EEE. EASL recommendations on treatment of hepatitis C 2016. *J Hepatol*. 2017;**66**(1):153–94. doi: 10.1016/j.jhep.2016.09.001. [PubMed: 27667367].
14. Hezode C, Colombo M, Bourliere M, Spengler U, Ben-Ari Z, Strasser SI, et al. Elbasvir, grazoprevir for patients with hepatitis c virus infection and inherited blood disorders: A phase III study. *Hepatology*. 2017;**66**(3):736–45. doi: 10.1002/hep.29139. [PubMed: 28256747].

15. Biliotti E, Palazzo D, Serani M, Silvestri AM, Volpicelli L, Esvan R, et al. Interferon free antiviral treatment of chronic hepatitis C in patients affected by beta-thalassemia major. *Ann Hematol*. 2017;**96**(6):1043–5. doi: 10.1007/s00277-017-2986-x. [PubMed: 28378040].
16. Mangia A, Sarli R, Gamberini R, Piga A, Cenderello G, Piazzolla V, et al. Randomised clinical trial: sofosbuvir and ledipasvir in patients with transfusion dependent thalassaemia and HCV genotype 1 or 4 infection. *Aliment Pharmacol Ther*. 2017;**46**(4):424–31. doi: 10.1111/apt.14197. [PubMed: 28660640].
17. Nagral A, Sawant S, Nagral N, Parikh P, Malde P, Merchant R. Generic direct acting antivirals in treatment of chronic hepatitis c infection in patients of thalassemia major. *J Clin Exp Hepatol*. 2017;**7**(3):172–8. doi: 10.1016/j.jceh.2017.08.002. [PubMed: 28970702].
18. Sinakos E, Kountouras D, Koskinas J, Zachou K, Karatapanis S, Triantos C, et al. Treatment of chronic hepatitis C with direct-acting antivirals in patients with beta thalassaemia major and advanced liver disease. *Br J Haematol*. 2017;**178**(1):130–6. doi: 10.1111/bjh.14640. [PubMed: 28439915].
19. Di Marco V, Bronte F, Cabibi D, Calvaruso V, Alaimo G, Borsellino Z, et al. Noninvasive assessment of liver fibrosis in thalassaemia major patients by transient elastography, (TE) lack of interference by iron deposition. *Br J Haematol*. 2010;**148**(3):476–9. doi: 10.1111/j.1365-2141.2009.07996.x. [PubMed: 19930183].
20. Minola E, Prati D, Suter F, Maggiolo F, Caprioli F, Sonzogni A, et al. Age at infection affects the long term outcome of transfusion associated chronic hepatitis C. *Blood*. 2002;**99**(12):4588–91. doi: 10.1182/blood-2001-12-0192. [PubMed: 12036892].