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Micro-elimination of Hepatitis C Virus Infection in Thalassemic Patients

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ABSTRACT

Background and objectives: We aimed to deploy an intra-hospital Hepatitis C Virus (HCV) micro-elimination project for thalassemic patients in collaboration with 2 pediatric departments and 4 transfusion units. This initiative took place between 2013-2022 and included various HCV regimens according to existing treatments and reimbursement criteria per period. Methods: HCV screening was performed at the Transfusion units and Pediatric departments. Following HCV diagnosis, thalassemic patients were referred to our Hepatology department for HCV-RNA and genotype examination, evaluation of liver fibrosis and finally to administer treatment. Results: In total, 119 patients were treated with direct-acting anti-viral agents (DAAs) in our center. SVR was achieved in 110/119 (92.4%) with the first line DAAs available. The SVR rates were not significantly associated with treatment experience, the presence of cirrhosis or liver iron concentration values. Treatment was generally well tolerated, and no significant interactions were recorded between DAAs and chelation agents or other co-medications. All patients who failed in the 1st line DAAs received 2nd line treatment and achieved SVR. Conclusions: Close collaboration between hematologists and hepatologists facilitates HCV diagnosis and access to effective and safe treatments for thalassemic patients. Micro-elimination projects for this population should be a priority on the road to Global HCV elimination.

Keywords: HCV, elimination, thalassemia, DAAs.

INTRODUCTION

In recent years, life expectancy of patients with beta Thalassemia Major has improved significantly mostly due to advances in iron chelation treatment, resulting in the reduction of heart-related mortality [1-2]. However, liver disease mainly related to chronic Hepatitis C virus (HCV) infection and iron overload is currently considered a major health burden for these patients [3-5]. Blood transfusions consist the prevalent cause of high HCV infection rate in thalassemic patients [6]. In Greece, previous epidemiological studies reported that 40-70% of the thalassemic population developed chronic HCV infection as a result of contaminated blood products before the establishment of HCV screening in transfusion units across the country [7-8].

During the interferon era, HCV treatment was considered a challenge for thalassemic patients due to low efficacy rates and most importantly due to low tolerability and increased need for transfusions [9-10]. The availability of Direct Acting Antivirals (DAAs) changed radically the therapeutic landscape of HCV treatment and provided the opportunity to treat the thalassemic patients effectively and with minimum adverse events [11]. In light of these advances, the World Health Organization (WHO) set a strategy to achieve the worldwide elimination of HCV infection until 2030[12]. This elimination plan included micro-elimination strategies targeting specific populations such as HIV co-infected patients, IV drug users and thalassemic patients. Micro-elimination projects can be achieved more easily than elimination in the general population, provided that the necessary stakeholders/health units are involved, and a well-organized plan is implemented [13].

First generation DAAs (telaprevir and boceprevir) became available in Greece in 2011, but their tolerability profile was not acceptable for patients with thalassemia [14]. In the following years, newer antiviral agents such as sofosbuvir and simeprevir received indication for HCV treatment but they were, initially, reimbursed only for cirrhotic patients. (Figure 1) [15]. In July 2017, the Hellenic National Plan for Hepatitis C was officially adopted by the Greek Minister of Health [16]. According to this plan, DAA treatment was provided by the National Health system for all thalassemic patients regardless of fibrosis stage.

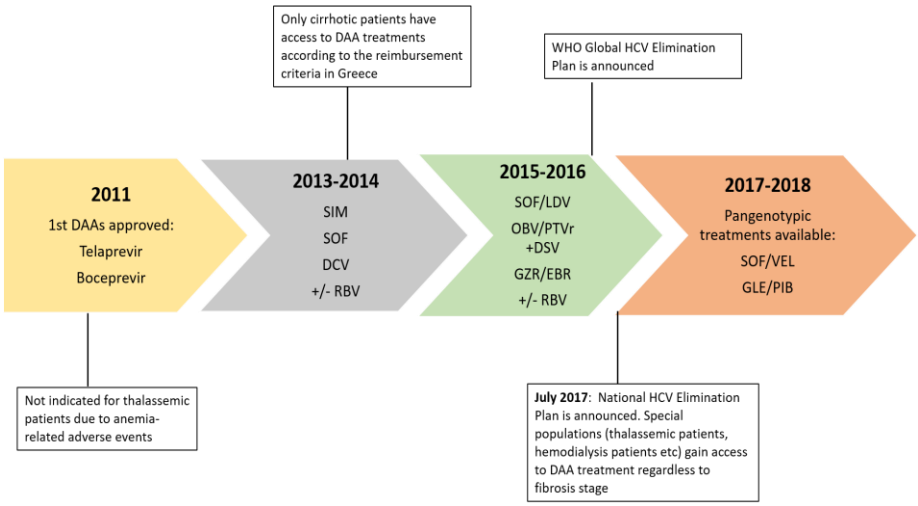

Figure 1: Direct Acting Antivirals timeline in HCV treatment and reimbursement criteria affecting thalassemic patients in Greece from 2011 to 2018. OBV; ombitasvir PTVr; paritaprevir/ ritonavir, DSV; dasabuvir. SOF; sofosbuvir, DCV; daclatasvir, LDV; ledipasvir, VEL; velpatasvir, SIM; simeprevir, GZR; grazoprevir, EBR; elbasvir, GLE; glecaprevir, PIB; pibrentasvir, RBV; ribavirin.

Our study aims to describe the strategic model followed to achieve HCV micro-elimination.

MATERIALS AND METHODS

Every HCV micro-elimination project is based on three key steps: a) screening, b) linkage to care and c) access to effective treatment [13]. A network of 6 thalassemia units acting as referring centers and a Liver Reference center was established. All patients in the referring centers had a long-term follow up with frequent serological screening for viral hepatitis.

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The outpatient Liver Unit department at Hippokration General Hospital of Athens, has been acting as a Liver Reference center in collaboration with the referring units for evaluation of thalassemic patients with either liver disease, hepatic iron overload and/or chronic HCV infection. All the patients with positive serologic anti-HCV was further evaluated for HCV viral load and HCV genotype testing. Imaging studies including fibrosis evaluation (liver elastography) and liver ultrasound were performed (Figure 2). Liver fibrosis evaluation was performed in our center using FibroScan (Echosens, Paris — France), considering cut-off of 7 kPa for mild fibrosis and of 12.5 kPa for cirrhosis [18]. After completion of the screening evaluation, the patients were offered treatment with DAAs. All thalassemic patients that received DAA treatment for HCV at our outpatient Hepatology Department between 2013 and 2022 were included in the study. An informed consent was provided by every patient before their inclusion in the study. DAA treatment was selected based on the chronological availability of HCV regimens and on the HCV treatment Guidelines of the European Association for the Study of the Liver (EASL) according to HCV genotype, fibrosis stage, previous treatment history, viral load, patient comorbidities and drug-drug interactions [17].

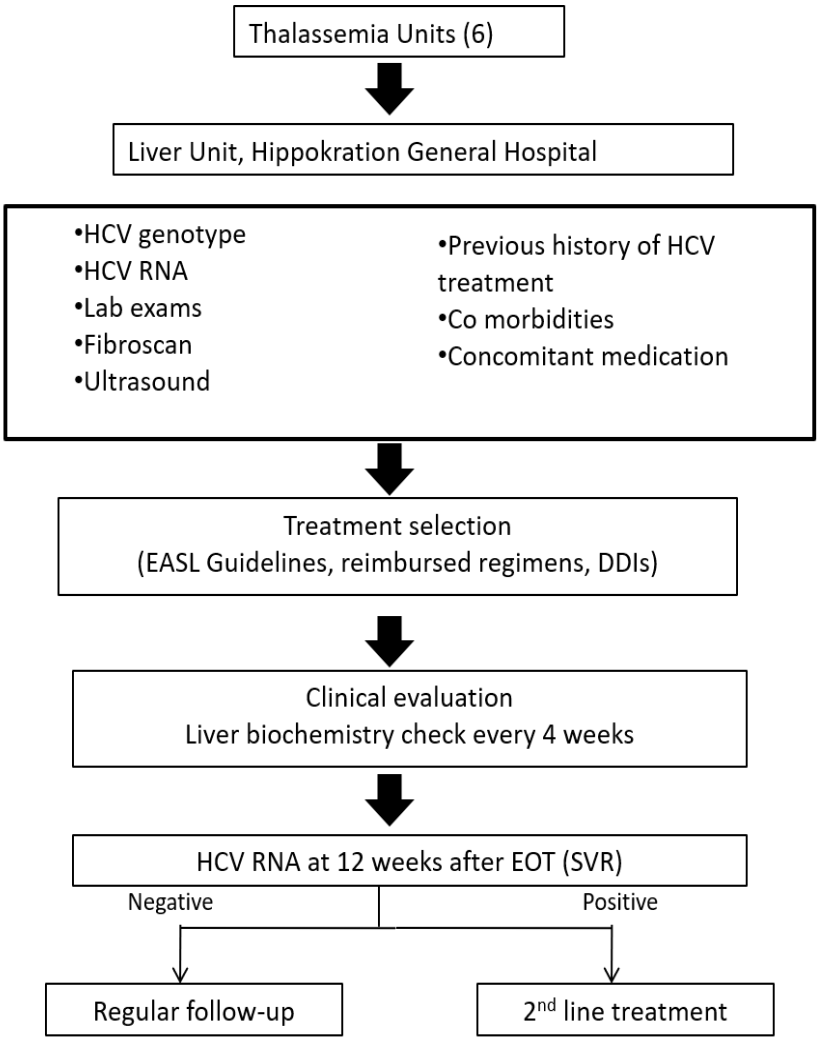

Figure 2: Management cascade from diagnosis to Hepatitis C virus (HCV) treatment. EASL; European Association for the Study of the Liver, DDIs; drug-drug interactions, EOT; end ot treatment, SVR; sustained virologic response.

Blood exams, including standard hematological and biochemical parameters were performed at baseline and every 4 weeks until the end of treatment. Viral load was examined at baseline and 12 weeks after the end of treatment. Sustained virologic response (SVR) was defined as undetectable HCV-RNA by a quantitative real time PCR with a limit of detection of 15 IU/Ml 12 weeks after the end of treatment. Hepatic iron overload was evaluated at baseline with T2* magnetic resonance imaging (MRI) and the conversion from T2* to liver iron concentration (LIC) was performed using the formula 0.202 + 25.4/T2*[19]. The number of transfusions per month during anti-viral treatment was recorded for every patient that was included in the study. All patients underwent regular physical examination every 4 weeks while receiving DAAs and any adverse event was immediately recorded.

STATISTICAL ANALYSIS

Continuous variables were presented as median (interquartile range) means +/- standard deviation as appropriate. Pearson chi-square test was applied to examine association between categorical variables. Mann Whitney test was performed to check for associations between LIC values, ferritin levels and the probability of SVR. Wilcoxon test was used to compare ALT and AST levels between baseline and 12 weeks after treatment. P values < 0.05 were considered significant.

RESULTS

Patient Characteristics

A total of 119 thalassemic patients who received DAA treatment from 2015 to 2022 were included in the study. Their baseline characteristics are summarized in Table 1. The most frequent genotype was 1b (37%), followed by genotype 4 (27,7%). The genotypic distribution of HCV in thalassemic patients depicts the respective distribution in the Greek population in the early 90's before the introduction of blood donor screening for HCV [20-21]. Interestingly, despite the young of their age, almost half of the patients (49.6%) were cirrhotic. Chelation treatment was generally effective since liver and heart iron overload parameters were favorable in most patients (Table 1).

Table 1: Patient Characteristics

Median age, years (range)	46, (20-78)
Male sex, n (%)	57 (47.9%)
HCV genotype, n (%)	
1a	13 (10.9%)
1b	38 (31.9%)
2	12 (10.1%)
3	23 (19.3%)
4	33 (27.7%)
Fibrosis stages n (%)	
1	17 (14.3%)
2	13 (10.9%)
3	29 (24.4%)
4	60 (50.4%)
Previous treatment	
Naïve	39 (32.8%)
Pegylated Interferon +/- Ribavirin	80 (67.2%)
Median HCV RNA, IU/ML (range)	650.000 (2.000-88.300.000)
Median ferritin levels, range (μg/L)	400 (48-6.000)

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LIC, (mg Fe/g d.w.), n (%)	
≤1.8	42 (35.3%)
1.9 - 7	68 (57.1%)
7.1 – 15	7 (5.9%)
>15	2 (1.7%)
Cardiac T2* (ms)	
>20	98 (82.4%)
14-20	10 (8.4%)
8-14	8 (6.7%)
<8	3 (2.5%)

HCV; Hepatitis C virus, LIC; Liver iron concentration

Efficacy

One hundred and nineteen (119) patients received DAA treatment for chronic HCV infection. The most frequently administered regimens included sofosbuvir/ledipasvir +/- ribavirin (RBV) (24/119, 20.2%) sofosbuvir/daclatasvir (19/119, 15.9%), sofosbuvir/velpatasvir +/- RBV (19/119, 15.9%), ombitasvir/paritaprevir/ritonavir +/- RBV (16/119 (13.4%) and sofosbuvir/simeprevir (15/119, 12.6%). Twenty-one patients (17.6%) in total received pangenotypic treatments. Analytic description of the administered DAA regimens is provided in Figure 3. RBV was used in 27/119 (22.7%). Treatment duration was 12 weeks for 104 patients (87.4%) and 24 weeks for 15 patients (12.6%). SVR was achieved in 110/119 patients (92.4%). Treatment failure was recorded in 9/119 (7.6%). Their characteristics are described in Table 2. All patients who failed had received DAA combinations that are no longer recommended by the EASL Guidelines. Especially the combinations of sofosbuvir/RBV and simeprevir/RBV consist old regimens with inferior efficacy rates comparing to the latest DAA treatments and are no longer available for prescription in Greece. The 9 patients who did not achieve SVR, received 2nd line DAA treatment: 2 received sofosbuvir/ledipasvir, 2 sofosbuvir/velpatasvir plus ribavirin and 5 received the currently indicated triple salvage therapy with sofosbuvir/velpatasvir/voxilaprevir. All patients achieved SVR with 2nd line treatment. Interestingly, there was no record of treatment failure in 21 patients who received the pangenotypic treatments.

Table 2: Characteristics of patients who failed Direct Antiviral Agent (DAA) treatment.

	Genotype	Fibrosis stage	Treatment experience	1stDAA treatment	2nd DAA treatment	LIC (mg Fe/g d.w.)	Ferritin (μg/L)
Patient 1	1b	4	naive	SOF/RBV	SOF/LDV	1.32	350
Patient 2	1b	4	naive	SOF/RBV	SOF/LDV	1.18	560
Patient 3	1b	2	PegIFN/RBV	SOF/SIM	SOF/VEL+ RBV	1.03	625
Patient 4	2	3	PegIFN/RBV	SOF/RBV	SOF/VEL+ RBV	1.2	535
Patient 5	1b	4	PegIFN/RBV	SOF/SIM	SOF/VEL/VOX	1.12	1900
Patient 6	4	4	PegIFN/RBV	SOF/DCV	SOF/VEL/VOX	1	817
Patient 7	1b	4	PegIFN/RBV	SOF/SIM	SOF/VEL/VOX	1.18	550
Patient 8	1b	4	naive	SOF/LDV + RBV	SOF/VEL/VOX	2.3	750
Patient 9	1a	3	PegIFN/RBV	OBV/PTVr +DSV+RBV	SOF/VEL/VOX	3.6	667

OBV; ombitasvi, r PTVr; paritaprevir/ ritonavir, DSV; dasabuvir, SOF; sofosbuvir, DCV; daclatasvir, LDV; ledipasvir, VEL; velpatasvir, RBV; ribavirin, PegIFN; pegylated interferon, SIM; simeprevir VOX; voxilaprevir LIC; Liver iron concentration

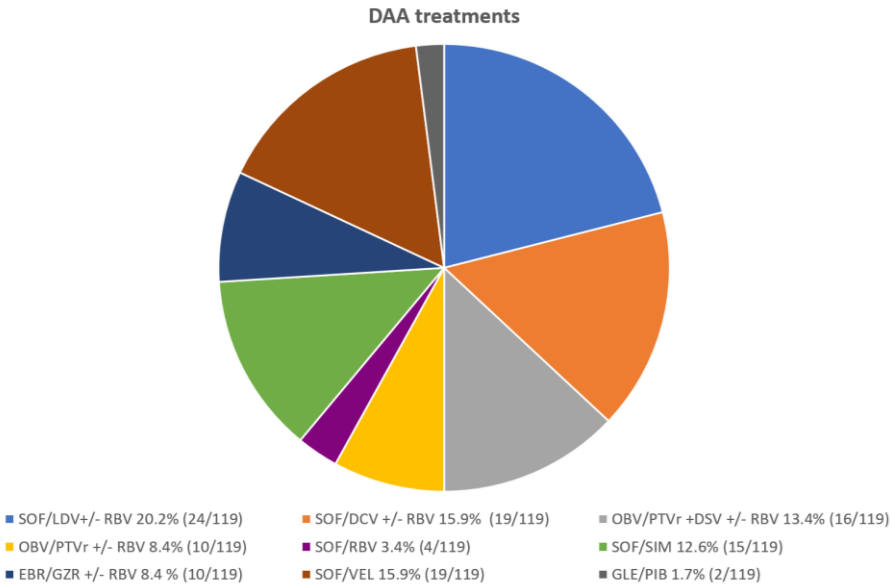

Figure 3: Direct Acting Antivirals distribution as administered in the study population. OBV; ombitasvir PTVr; paritaprevir/ ritonavir, DSV; dasabuvir, SOF; sofosbuvir, DCV; daclatasvir, LDV; ledipasvir, VEL; velpatasvir, RBV; ribavirin, SIM; simeprevir VOX; voxilaprevir, EBR; elbasvir, GZR; grazoprevir, GLE; glecaprevir PIB; pibrentasvir.

Previous treatment experience did not affect the probability of SVR (Pearson chi-square p=0.53). Similarly, SVR rate was not significantly associated with the presence of cirrhosis (Pearson chi-square, p=0.25) nor with LIC values (Mann-Whitney test p=0.22) and ferritin levels (Mann-Whitney test p=0.15).

HCV treatment had a positive effect on the transaminase levels of 114 patients who achieved SVR (Figure 4).

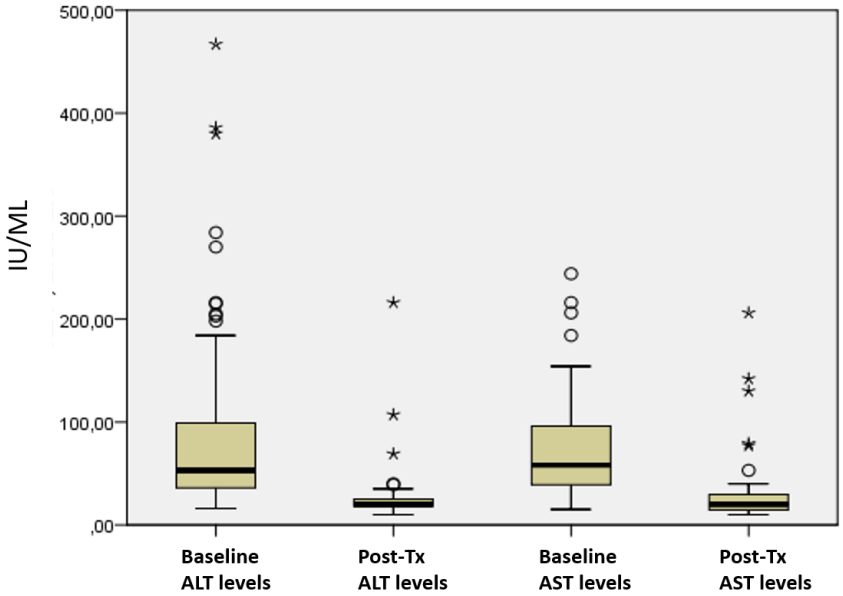

Figure 4: Post-treatment changes in transaminase levels. Tx; treatment, AST; aspartate tranferase, ALT; alanin tranferase.

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Specifically, median alanine aminotransferase (ALT) levels decreased significantly 12 weeks after the end of treatment (median: 20, Q25-75:18-25 IU/ML) comparing to baseline levels (median:53, Q25-Q75:35-106 IU/ML), ($p<0.001$). Similarly, aspartate transaminase (AST) levels were significantly lower at 12 weeks post-treatment (median:21, Q25-75:14-29 IU/ML) comparing to pre-treatment levels (median:58, Q25-75:38-97 IU/ML), ($p<0.001$).

Safety

DAA treatment was well tolerated without any serious adverse event or drug discontinuation during the study. The most frequently reported adverse events included headache (4/119, 3.6%) and nausea (3/119, 2.5%), while one patient reported pruritus during treatment with ombitasvir/paritaprevir/ ritonavir. In 20/27 patients who received RBV, a decrease of time interval from 10-15 to 7-10 days between transfusions was reported by the thalassemia units. The patients' comorbidities included mainly cardiovascular diseases such as arterial hypertension in 22/119 (18%), atrial fibrillation in 6/119 (5%), heart failure in 2/119 (2%) and other arrythmias in 4/119 (3%), hypothyroidism in 5/119 (4%) and chronic kidney disease in 3/119 (2%). There was no report of any significant deterioration of the above comorbidities during HCV treatment.

Drug-drug Interactions

No significant drug-drug interaction (DDI) between DAAs and chelation agents was reported. The administered chelation treatments included deferoxamine in 13/119 (10.9%) patients, deferiprone in in 48/119 (40.3%), deferasirox in 11/119 (9.2%), and combinations of 2 agents in 47/119 (39.5%). All chelation agents were continued during HCV treatment without any need for dose adjustments.

Apart from chelation treatments, the study population received various regimens for the comorbidities that are mentioned above.

DISCUSSION

In this study, we presented an intra-hospital micro-elimination project in thalassemic patients with chronic HCV infection that was developed and completed between 2013-2022 following the entrance of DAAs in the HCV treatment landscape. All 119 patients of the study received DAA treatment and achieved SVR.

The concept of HCV micro-elimination in specific populations was introduced by the WHO in their 2016 Global health sector strategy on viral hepatitis (GHSS) when the first targets for worldwide HCV elimination were set [12]. The Greek national elimination plan [16] refers to micro-elimination strategies as more pragmatic approaches on the road to HCV elimination and defines specific targets for populations with high burden of disease such as the HIV co-infected, patients on hemodialysis and the thalassemic patients. Several successful examples of micro-elimination strategies have been developed in various countries [22-23]. Byrne et al. recently reported a micro-elimination project in HIV co-infected people who inject drugs (PWID) in a health board in Scotland [22]. Diagnosis rates, access to treatment and SVR rates significantly increased in the last years thanks to this initiative. Giuliani et al. also described a teat-and treat intervention that resulted in HCV micro-elimination in two prisons in Milan [23]. Both studies identify quick, universal HCV testing, immediate referral to care and limitless access to DAA treatment as key factors for the accomplishment of micro-elimination targets.

Our micro-elimination strategy was based on the long-term close collaboration of our outpatient Liver Unit with 6 large thalassemic units. Our efforts to treat thalassemic patients with chronic HCV infection had started from the interferon era despite the already mentioned difficulties of these regimens for this population in terms of adverse effects and low efficacy rates [24]. However, once the first DAA treatments became available, a specific plan which included evaluation of HCV viral load, HCV genotype, fibrosis stage with fibroscan, ultrasound and appropriate treatment. All patients were aware of the existing treatments and showed strong engagement, high compliance rates and willingness to receive the DAAs. Close follow-up was facilitated by the fact that all patients appeared every 10 days in their thalassemia units according to their transfusion plan.

Interestingly, our micro-elimination project was conducted in two different phases depending on existing restrictions of access to treatment. In the period between 2015 and 2017, only cirrhotic patients could access the expensive DAA treatments, a factor that possibly explains the high proportion of patients with advanced fibrosis in our study. Additionally, the DAA regimens that were administered, changed significantly from 1st generation treatments such as sofosbuvir/RBV and simeprevir/sofosbuvir which are no longer recommended by EASL Guidelines [17] to the latest pangenotypic regimens during the study period. These developments practically divide our research in a first period of difficult-to-treat cirrhotic patients who received older DAA regimens with inferior efficacy [25] and a second period of patients with lower fibrosis stages who received new even more efficient DAA treatments [25]. Nevertheless, SVR rates were very high (>90%) across the study population regardless of the fibrosis stage and the administered regimen. It should be also noted that no treatment failure was recorded in the patients that received the latest pangenotypic treatments. Moreover, other patients' characteristics such as treatment experience or severe iron overload did not seem to affect the efficacy of DAAs in contrast to the limited efficacy of IFN-based schemes in these cases [26]. Similar reports of high DAA efficacy regardless of patients' parameters have been published by other investigators as well [27-28]. The above results indicate that DAA therapy should be considered even in patients with severe iron overload or history of treatment failure as it may provide SVR rates close to 100%. Furthermore, in cases of DAA failure, the combination of sofosbuvir/voxilaprevir/velpatasvir should be used as 2nd line treatment with excellent SVR rates as suggested by the current International Guidelines [17,29].

DAA treatment was generally well-tolerated despite the particularity and the comorbidities of the study population. There was no report of severe adverse events, while co-administration of RBV with DAAs increased the need for transfusions in 20 patients without any drug discontinuation. Treatment with RBV was well-tolerated possibly due to the short duration of DAA schemes and the absence of the myelosuppressive effect of interferon [30-31]. In terms of DDIs, all chelation agents were continued during DAA treatment without any significant interaction. Although there are no specific studies, deferiprone is the only chelation agent with available positive recommendation for co-administration with DAAs in www.hep-druginteractions.org/checker based on drug metabolism. However, there is a randomized placebo-controlled study by Hezode et al. and published real-life data that support the co-administration of chelators with DAAs without any report for significant interactions [30-33].

Following achievement of SVR, long term-follow up should be continued for every cirrhotic patient and especially for thalassemic patients [34]. Hepatocellular carcinoma (HCC) is a

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frequent cause of death and often presents with aggressive biological behavior in these patients [35-36]. The clearance of HCV, along with effective iron chelation therapy which minimizes liver iron overload will probably have a positive effect on liver mortality and HCC development. All patients remained on HCC surveillance program irrespective of the presence of cirrhosis with Ultrasound examination and alpha fetoprotein (AFP) levels every 6 months according to [37]. This surveillance program for HCC was established in the last decade through our close collaboration with the referring units and includes all patients with thalassemia regardless of SVR achievement.

CONCLUSIONS

After the entrance of DAAs in HCV treatment, thalassemic patients consist an easy-to treat population in terms of high efficacy and tolerance according to our center's experience. The significant liver mortality rates in this patient group make HCV clearance mandatory. In contrast to the general population, HCV diagnosis, linkage to care and access to treatment are achievable in thalassemic patients since most of them are closely followed at their transfusion units. The effective collaboration between hematologists and hepatologists is a key for positive patient outcomes.

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