Hashem et al. Egyptian Liver Journal (2021) 11:48
https://doi.org/10.1186/s43066-021-00117-4

Egyptian Liver Journal

ORIGINAL RESEARCH ARTICLE Open Access

Microelimination of hepatitis C in patients with chronic hemolytic anemias: a single-center experience

Walaa M. Hashem[1], Manal Hamdy El-Sayed[2], Ossama A. Ahmed[1], Hany M. Dabbous[3], Mohamed Kamal Shaker[3], Ahmed Fouad Sherief[3], Mary Gamal Naguib[4], Shereen Abdel-Monem Ibrahim[5] and Ahmed Mansour[1*]

Abstract

Background: Patients with chronic hemolytic anemias (CHA) are at a high risk for transfusion-transmitted infections. Various studies in Egypt have shown a prevalence of hepatitis C virus (HCV) infection in 24–37% of those patients. Elimination of hepatitis C virus (HCV) in patients with CHA would prevent early progression of liver disease. In this study, we aimed to assess the efficacy, safety, and tolerability of sofosbuvir (SOF) and daclatasvir (DAC) in the special population of HCV-infected patients with CHA. In this prospective study, 21 consenting hepatitis C patients were recruited and treated using ribavirin-free SOF/DAC regimen for either 12 or 24 weeks according to categorization of patients into easy or hard-to-treat in accordance with the national protocols. Sustained virological response was assessed by RT-PCR for HCV-RNA at 12 weeks post-treatment (SVR12). Any treatment-related adverse events were noted.

Results: All patients were adherent to treatment with no discontinuation of therapy. SVR12 was achieved in 19 out of 21 patients (90.5%). There was a significant improvement in levels of ALT ($p<0.009$) after completion of therapy. On the other hand, the hemoglobin, total bilirubin, and ferritin levels showed a non-significant difference ($p<0.501$, $p<0.542$, and $p<0.339$, respectively). Moderate adverse events were observed in 2 out of 21 patients (9.5%), including sickling crisis and hepatic decompensation.

Conclusion: The results of this study substantiate the favorable efficacy, safety, and tolerability of ribavirin-free direct-acting antivirals (DAAs) in the special population of HCV-infected patients with CHA. Micro-elimination of HCV in special patient populations allows for pragmatic delivery of care to patients with co-morbid conditions who are in most need for treatment and allows for achievement of global elimination of HCV worldwide.

Keywords: Microelimination, Hepatitis C, Anemia, Hemolytic, Thalassemia, Antiviral agents, Daclatasvir, Sofosbuvir

Background

CHA is a common blood disorder which occurs either due to hereditary or acquired causes [1]. Survival of most of this group of patients depends mainly upon regular blood transfusion which makes them at risk for iron overload and transfusion-transmitted infections [2].

Hepatitis C is considered to be one of the major transfusion-transmitted infections which represents a serious public health problem worldwide [3]. According to the World Health Organization (WHO), about 71 million people in the world are chronically infected with HCV, with the prevalence of this infection varying throughout the world [4].

Various studies have reported the prevalence of HCV in patients with thalassemia in different countries, e.g., 16.7 % in India, 22.4% in Malaysia, and 63.8% in Iran [5].

* Correspondence: ahmad_magdy@med.asu.edu.eg
[1]Gastroenterology, Hepatology and Internal Medicine Department, Ain Shams University, Cairo, Egypt
Full list of author information is available at the end of the article

In Egypt, studies conducted in different regions showed that the prevalence ranged between 24 and 37% [2].

Pegylated interferon-α (PEG-INF) and ribavirin (RBV) was the only treatment available for HCV infection for several years. It showed a moderate efficacy in patients with chronic hemolytic anemias especially those with thalassemia. Its use was also limited by poor tolerance, and some concerns about RBV-induced hemolysis [6].

The advent of DAAs has brought about a sudden renaissance in the treatment of chronic HCV infection with SVR rates now routinely >90%. The shorter treatment duration and fewer side effects make DAAs the current standard of care for treatment of HCV in adults [7]. According to recent guidelines, patients with chronic hemolytic anemias should be treated with DAAs, preferably by RBV-free regimens [8].

The efficacy of the new DAAs regimens helped WHO to adopt its first Global Health Sector Strategy on Viral Hepatitis in 2016. Its goal was to simply combat hepatitis by calling for the elimination of HCV as a public health threat by 2030. The strategy defined elimination as an 80% reduction in new HCV infections and a 65% reduction in HCV mortality [9].

The most accepted pragmatic approach was to break down the national elimination goals into smaller subgoals uniquely tailored for individual populations, for which treatment and prevention strategies can be delivered more quickly and efficiently. This concept was known as “micro-elimination”. Among these individual populations are patients with hemolytic anemias [10].

Micro-elimination strategy was accepted globally, and most high-income countries have already begun its implementation [11]. Other countries including Egypt, Iceland, Portugal, and Spain have also undertaken such strategy as a step to achieve broader elimination goals aimed at the general population [10].

Limited studies addressed the efficacy and safety of the currently available DAAs in this special population. Therefore, this study aimed to assess the efficacy and safety of SOF/DAC regimen in patients with CHA and HCV infection.

Methods

This was a prospective study of patients diagnosed with chronic HCV infection who presented to our institution to receive therapy with DAAs between January 2018 and January 2020. Out of 9500 registered patients, 171 (1.8%) were diagnosed with co-morbid hematological disorders; among those, 21 had chronic hemolytic anemias. Patients with decompensated liver disease, hepatitis B virus (HBV), or human immune-deficiency virus (HIV) co-infection and those with underlying malignancies were excluded. An informed written consent was obtained from all patients before inclusion in this study. The study was approved by the Ethical Review Board of our institution (Reference Number: FMASU M S 67/2019). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

The demographics of enrolled patients, type of hemolytic anemia, treatment status (naïve or experienced), frequency of blood transfusion, and type of iron chelators before treatment were all recorded both electronically and in a patient report form.

Baseline investigations included complete blood count (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total and indirect bilirubin, serum albumin, international normalization ratio (INR), serum creatinine, alpha-fetoprotein, serum ferritin level, and pelvi-abdominal ultrasound, in addition to non-invasive assessment of liver stiffness by FIB4 and APRI scores. HCV viral load was determined by real-time polymerase chain reaction (RT-PCR) assay.

All patients received SOF 400mg and DAC 60mg daily. None of the patients received RBV in addition to their treatment regimen to avoid the hematological adverse events. The treatment duration ranged between 12 and 24 weeks according to baseline patients’ categorization as either easy or hard to treat in accordance with the national protocols.

Patients were categorized as hard to treat if meeting any of the following criteria: PEG-INF treatment-experienced (TE), total bilirubin ≥1.2 mg/dl, serum albumin ≤3.5 g/dl, INR ≥1.2, or platelet count <15,0000/mm^3. The easy to treat group included 8 patients who were treated with SOF/DAC for 12 weeks. The difficult to treat group included 13 patients who were treated with SOF/DAC for 24 weeks.

Patients underwent a 4-weekly follow-up of CBC, serum total and indirect bilirubin, ALT, AST, INR, and serum creatinine. The monthly blood transfusion requirements, as well as any treatment-related adverse events, were recorded every visit. Twelve weeks after the end of SOF/DAC treatment, patients were tested for SVR12 HCV-RNA, serum ferritin level, a pelvi-abdominal ultrasound, and non-invasive assessment of liver fibrosis by FIB-4 and APRI. Change in blood transfusion and iron chelators requirements compared to baseline was also recorded.

The primary aim of our study was to assess the effectiveness of SOF/DAC regimen in this special population of patients by achievement of SVR as defined by undetectable HCV RNA twelve weeks after the end of therapy. The secondary aim was to study the safety and tolerability of DAAs in this special population of patients. All treatment-related adverse events were noted.

All results were collected, tabulated, and statistically analyzed using computer software (IBM SPSS ver. 22).

Descriptive statistical tests of frequency, mean, and standard deviation (SD) were used to describe the obtained data. Moreover, different variables were compared before and after treatment using paired T-test (for parametric data) and related-sample Wilcoxon signed-rank test (for non-parametric data).

Results

Study population

This study included 21 patients with CHA recruited from our institution. These patients included 11 females (52.4%) and 10 males (47.6%), with age ranging between 18 and 62 years (median 33 years). Most of the patients were diagnosed with β-thalassemia (12 patients with thalassemia major [57.1%] and 6 patients with thalassemia intermedia [28.6%]). All patients were treatment-naïve apart from one patient who had been previously treated with PEG-INF (95.2% vs 4.8%, respectively). All patients were either non-cirrhotic or compensated liver cirrhosis (Child A/B). Decompensated cirrhotic patients were excluded from the study. The rest of patients' characteristics and baseline laboratory investigations are summarized in Tables 1 and 2.

Patients received iron chelator therapy as follows: desferoxamine was given intravenously at a dose of 40–50 mg/kg/day over 8–12 h for 5–7 days/week. Deferiperone was given orally at an initial dose of 75mg/kg/day, and a maximum dose of 99 mg/kg/day. The total daily dose was divided twice or thrice daily. No dose adjustment was needed for patients with mild or moderate impairment of hepatic function. Deferasirox was given orally at a dose of 10 mg/kg/day with a maximum dose of 20 mg/kg/day. No dose adjustment was required in patients with Child A, while the dose was decreased by 50% in patients with Child B.

Treatment response

Nineteen out of 21 patients (90.5%) achieved SVR 12 weeks after the end of DAA therapy. The only treatment-experienced (TE) patient in the study achieved SVR (100%), while 18 out of 20 treatment-naïve patients (TN) achieved SVR (90%). According to treatment duration, all 8 patients who received treatment for 12 weeks achieved SVR (100%), while 11 out of 13 patients who received treatment for 24 weeks achieved SVR (84.6%). Both non-responders were β-thalassemia major patients with advanced liver disease treated with SOF 400 mg and DAC 60 mg for 24 weeks. They were ineligible to receive RBV to avoid increased frequency of blood transfusion (mean Hb 7.65 g/dl).

The first non-responder was a 33-year-old female patient who presented with baseline HCV-RNA of 1,458, 963 copies/ml, elevated transaminases (ALT 61 IU/L, AST 116 IU/L), serum ferritin 577 ng/ml, and advanced liver fibrosis (fibroscan liver stiffness 9.6 kPa, F3). She was kept on Deferasirox for iron chelation. The patient was retreated using ritonavir-boosted paritaprevir/ombitasvir and SOF for 24 weeks due to RBV ineligibility and achieved SVR.

The second non-responder was a 32-year-old male patient who presented with baseline HCV-RNA >4 million copies/ml, elevated transaminases (ALT 66 IU/L, AST 99 IU/L), serum ferritin 1670 ng/ml, and advanced liver fibrosis (fibroscan liver stiffness 34.8 kPa, F4). He was kept on deferiprone for iron chelation. The patient was retreated with SOF, DAC, and simeprevir for 24 weeks, and achieved SVR.

Among the studied group, the hemoglobin and ferritin levels did not change after treatment from baseline levels ($p<0.501$ and $p<0.339$, respectively). Similarly, the mean total serum bilirubin did not show a significant difference between baseline and post-treatment levels (2.62± 1.11 vs 2.49±1.48 mg/dl, respectively, $p<0.542$). However, ALT levels dropped significantly at the end of treatment compared to baseline levels (41.41± 24.02 IU/L vs 54.48 ± 22.9, respectively, $p<0.009$).

The non-invasive assessment of liver fibrosis pre- and post-treatment showed significant improvement in APRI (0.44±0.27 vs 0.32±0.22, $p<0.046$) but not in FIB-4 scores (0.78±0.7 vs 0.61±0.5, $p<0.175$) in this population.

The frequency of blood transfusion was assessed by regular monthly follow-up of patient-reported blood transfusion, followed by calculation of mean transfusion amount throughout treatment period and comparing it to baseline mean transfusion requirements. The frequency did not change in the majority of patients. At the end of the DAA treatment period, 12 patients (57.14%) had no change in their blood transfusion requirements and one patient (4.76%) had a decrease in his requirements, while 8 patients (38.1%) had an increase in their requirements, rising from 293.75 ml/month at baseline to 697.89 ml/month at the end of treatment period.

Similarly, the requirements for iron chelation therapy after the end of treatment showed no change among 15 patients (71.4%) and 4 patients (19%) had decreased requirements, while 2 patients (9.5%) had increased requirements.

Safety

Apart from minor adverse events, e.g., dizziness and anorexia (Table 3), one patient with β-thalassemia major who received SOF/DAC for 24 weeks experienced a severe adverse event necessitating immediate withholding of therapy. The patient presented with dyspnea and hepatic decompensation at week 16 and Child-Pugh score deteriorated from A5 to B7. Laboratory investigations revealed hypoalbuminemia (1.9 g/dl vs 3.7 g/dl at

Table 1 Baseline demographic, clinical, and laboratory data for enrolled patients with CHA and HCV infection (n=21)

Characteristics	Frequency (%)/mean±SD
Gender	
Male	10 (47.6%)
Female	11 (52.4%)
Age (years)	18–62 (median 33)
BMI (kg/m^2)	24.4±3.67
Treatment status	
Naïve	20 (95.2%)
Experienced	1 (4.8%)
Treatment duration	
12 weeks	8 (38.1%)
24 weeks	13 (61.9%)
Diagnosis	
β-Thalassemia major	12 (57.1%)
β-Thalassemia intermedia	6 (28.6%)
β-Thalassemia minor	1 (4.8%)
Sickle cell anemia	1 (4.8%)
Hemolytic anemia due to cryoglobulins and cold agglutinins	1 (4.8%)
Child-Pugh score	
A	13 (61.9%)
B	8 (38.1%)
Blood transfusion	
Regular	18 (85.7%)
Sporadic	2 (9.5%)
No	1 (4.8%)
Iron chelators	
No	9 (42.86%)
Deferoxamine	4 (19.05%)
Deferiprone	3 (14.28%)
Deferasirox	5 (23.81%)

Table 2 Comparison between baseline and end-of-treatment laboratory investigations among enrolled patients with CHA and HCV

Lab	Mean ± SD		Significance
	Baseline	End-of-treatment	
Hb (g/dl)	8.51±1.28	8.4±1.2	p<0.501
Ferritin (ng/ml)	1807.63±1480.36	1762.63±1918.7	p<0.339
T.Bil (mg/dl)	2.62±1.11	2.49±1.48	p<0.542
ALT (IU/l)	54.48±22.9	41.41±24.02	p<0.009
Albumin (g/dl)	4.09±0.48	4.3±0.5	p<0.182
INR	1.17±0.09	1.2±0.14	p<0.341
FIB-4	0.78±0.7	0.61±0.5	p<0.175
APRI	0.44±0.27	0.32±0.22	p<0.046

Table 3 Adverse events reported during treatment

Adverse event	Number (%)
No	16 (76.19%)
Dizziness	1 (4.76%)
Anorexia	1 (4.76%)
Sleepiness	1 (4.76%)
Menorrhagia	1 (4.76%)
Sickle cell crisis	1 (4.76%)
Decompensation	1 (4.76%)

baseline) and hyperbilirubinemia (2.6 mg/dl vs 1.9 mg/dl at baseline). A computed tomography of the chest revealed bilateral pleural effusion, and a small rim of pericardial effusion. The patient was admitted to the hospital for management and follow-up. All lab parameters improved thereafter, and the patient achieved SVR.

Another patient experienced a sickle cell crisis at week 12; vaso-occlusive painful crises with generalized severe bone pains and chest pain which resolved by intravenous fluid replacement therapy and packed RBCs. This patient had another episode of sickle cell crisis 3 month following the completion of DAA treatment, which increases the possibility of a non-treatment-related adverse event.

Discussion

HCV infection represents a major clinical health issue in patients with CHA. About 70–80% of infected patients develop chronic hepatitis and up to 20% progress to cirrhosis [12].

The introduction of DAAs has dramatically changed HCV treatment due to its high efficacy (>90%) and superior safety profile compared to INF-based therapy. Although limited data exist on the use of DAAs in hepatitis C patients with chronic hemolytic anemias, current guidelines recommend using DAAs in this group of patients [8].

The current study showed a high SVR of 90.5%, which agrees with other studies done on this special population of patients by Nagral and Alvi and their colleagues showing SVR of 100% using different DAA regimens including fixed dose combination of Ledipasvir (LED/SOF) with and without RBV, and fixed dose combination of Velpatasvir/SOF, in addition to SOF/DAC [7, 13].

Moreover, a large multi-center phase 3 study done on 156 patients with different inherited blood disorders including β-thalassemia and sickle cell anemia reported SVR of 93.5% using fixed dose combination of elbasvir/grazoprevir for 12 weeks [14]. This variability in the treatment regimens used further proves the efficacy of different DAA regimens in management of HCV in patients with CHA.

In contrast, the high SVR in our study differs from a multi-center study done by Di Marco et al. on 230 patients with thalassemia major, which showed very low SVR ranging from 37 to 62% across different HCV genotypes. The main explanation for this contradiction is due to the fact that this study used Peg-interferon (Peg-INF) and RBV not DAAs [15].

Our study achieved complete cure of a single patient with sickle cell anemia, agreeing with a study done by Moon et al. including 10 patients with SVR achieved in 9 patients and failure of only one patient due to drug non-compliance, although in that study, fixed dose combination of LED/SOF was used [16].

Our results therefore confirm that the advent of DAAs has revolutionized the treatment of CHC in subjects with CHA. Not only the rate of premature withdrawal because of adverse events has been reduced to zero while it was as high as 25% with INF-containing regimens, but also the achievement of SVR has dramatically increased from a range of 28 to 66% in patients under INF monotherapy, and from a range of 31 to 93% in patients treated with PEG-INF and RBV to results close to 100% in patients treated with DAAs [15].

This study showed that there was a statistically significant reduction in ALT at end-of-treatment, agreeing with other different studies on patients with thalassemia major ($p<0.009$) [8, 14, 17]. The significant drop in ALT paralleled the drop in the levels of HCV RNA. This could be attributed to the reduction in the liver parenchymal inflammation.

A prospective Indian study assessing the safety and efficacy of SOF-based DAAs including 29 thalassemic patients showed significant decline in serum ferritin levels after treatment despite an increase in transfusion requirements during treatment [18]. Similar results have been presented by Nagral, Alvi, Ponti, and their colleagues [13, 19, 20]. Similarly, the present study showed that there was a decline in serum ferritin at end-of-treatment although it was not statistically significant (1807.63±1480.36 vs 1762.63±1918.7 ng/ml, $p<0.339$). This decline could be due to the use of chelation therapy prior to initiation of DAA therapy to prevent iron overload.

The change in Hb levels was not statistically significant when compared pre- and post-treatment as the study conducted by Nagral and his colleagues [20].

The effect of new antivirals on blood consumption in our cohort was negligible, 38.1% of the patients experienced increase in blood requirements while the majority (57.14%) did not experience any change in transfusion requirements.

In the present study, most patients (71.4%) had no change in their iron chelator requirements, 4 patients (19%) had a decrease, while 2 patients (9.5%) had an increase in their requirements. This comes in accordance with other studies in which there was no significant difference in requirements of iron chelators when compared pre- and 3-month post-treatment [17, 20].

Most patients did not experience any side effects during treatment, and the side effects reported were negligible in comparison with those depicted in previous antiviral regimens including INF. The most relevant side effect was hepatic decompensation in one patient which necessitated treatment discontinuation.

Conclusion

RBV-free DAAs are considered safe, tolerable, and effective modalities in treatment of hepatitis C patients with CHA. Microelimination of HCV in special patients' populations is currently the accepted pragmatic approach to aid in achieving global goals for elimination of HCV worldwide. However, this study was limited by relatively small sample size, and absence of patients with decompensated liver cirrhosis. More studies are needed to address such aspects in the future.

Abbreviations

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CBC: Complete blood count; CHA: Chronic hemolytic anemia; DAAs: Direct-acting antivirals; DAC: Daclatasvir; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immune-deficiency virus; INR: International normalization ratio; LED: Ledipasvir; PEG-INF: Pegylated interferon-α; RBV: Ribavirin; RT-PCR: Real-time polymerase chain reaction; SOF: Sofosbuvir; SVR12: Sustained virological response at 12 weeks post-treatment; WHO: World Health Organization

Acknowledgements

None.

Declarations

.

Authors' contributions

WH formulated the research idea and shared in the data collection, analysis, and manuscript revision. ME supervised the data analysis and manuscript drafting. OA shared in the manuscript revision. HD, MS, and AS analyzed the collected data and revised the final manuscript. MN shared in the data collection and manuscript drafting. SI shared in the statistical analysis of collected data, together with manuscript revision. AM shared in formulation of research hypothesis, data processing, statistical analysis, and drafting of final manuscript. All authors have read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from corresponding author upon reasonable request.

Ethics approval and consent to participate

All subjects involved in the study signed an informed written consent to participate. The study was approved by the Ethical Review Board of our institution (Reference Number: FMASU M S 67/2019). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

Author details

[1]Gastroenterology, Hepatology and Internal Medicine Department, Ain Shams University, Cairo, Egypt. [2]Department of Paediatrics and Clinical Research Center, Ain Shams University, Cairo, Egypt. [3]Tropical Medicine Department, Ain Shams University, Cairo, Egypt. [4]Clinical Haematology and Internal Medicine Department, Ain Shams University, Cairo, Egypt. [5]Department of Clinical Pathology, Ain Shams University, Cairo, Egypt.

Received: 27 January 2021 Accepted: 2 June 2021
Published online: 09 June 2021

References

1. Haley K (2017) Congenital hemolytic anemia. Med Clin N Am 101:361–374
2. Mahmoud RA, El-Mazary AAM, Khodeary A (2016) Seroprevalence of hepatitis C, hepatitis B, cytomegalovirus, and human immunodeficiency viruses in multitransfused thalassemic children in Upper Egypt. Adv Hematol 2016:1–7. https://doi.org/10.1155/2016/9032627
3. Brown RS, Gaglio PJ (2003) Scope of worldwide hepatitis C problem. Liver Transpl 9(11)
4. WHO. Hepatitis C. 2019 [cited 2019 Nov 1]; Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c
5. Al-Sharifi L, Murtadha J, Shahad A, Mohammed Y, Sura J, Waleed Z, Raheeq M, Sura A, Ehab H, Shahad M, Abbas Q (2019) Prevalence of hepatitis B and C in thalassemic patients and its relation with type of thalassemia, frequency of blood transfusion, and spleen status. Med J Babylon 16(2):108. https://doi.org/10.4103/MJBL.MJBL_6_19
6. Casu S, Balestrieri C, Figorilli F, Onali S, Serra G, Chessa L, Lai ME (2014) P1155 safety and efficacy of PEG-IFNa2a and ribavirin for treatment of hepatitis C in Sardinian adult patients with thalassemia major: a single centre real life experience. J Hepatol 60(1):S468. https://doi.org/10.1016/S0168-8278(14)61315-5
7. Nagral A, Sawant S, Nagral N, Parikh P, Malde P, Merchant R (2017) Generic direct acting antivirals in treatment of chronic hepatitis C infection in patients of thalassemia major. J Clin Exp Hepatol 7(3):172–178 [cited 2019 Aug 8]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28970702
8. EASL Recommendations: Treatment of hepatitis C (2018) - EASL-The Home of Hepatology. European Association for the Study of the Liver. [cited 2019 Nov 1]. Available from: https://easl.eu/publication/easl-recommendations-treatment-of-hepatitis-c/
9. Hirnschall G, Programme GH. WHO | Global health sector strategy on viral hepatitis 2016-2021. WHO. 2016;(May 2015):1–5. [cited 2020 Aug 31] Available from: http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/
10. Lazarus JV, Wiktor S, Colombo M, Thursz M (2017) Micro-elimination – a path to global elimination of hepatitis C. J Hepatol 67:665–666 [cited 2020 Aug 31], Available from: https://pubmed.ncbi.nlm.nih.gov/28760329/
11. Fitzgerald C. Hepatitis C "effectively eradicated" in haemophilia patients who were given contaminated blood. [cited 2020 Aug 31]. Available from: https://www.thejournal.ie/hepatitis-c-3154653-Dec2016/
12. Minola E, Prati D, Suter F, Maggiolo F, Caprioli F, Sonzogni A, Fraquelli M, Paggi S, Conte D (2002) Age at infection affects the long-term outcome of transfusion-associated chronic hepatitis C. Blood 99(12):4588–4591 [cited 2019 Nov 1], Available from: http://www.ncbi.nlm.nih.gov/pubmed/12036892
13. Alvi MA, Arshad Cheema H, Saeed A, Batool S, Pakistan L, Cheema HA, Saeed A, Batool S (2018) Ribavirin free direct-acting antivirals in adolescents with hepatitis C and thalassemia. J Fatima Jinnah Med Univ 12:110–114
14. Hézode C, Colombo M, Bourlière M, Spengler U, Ben-Ari Z, Strasser SI, Lee WM, Morgan L, Qiu J, Hwang P, Robertson M, Nguyen BY, Barr E, Wahl J, Haber B, Chase R, Talwani R, Di Marco V (2017) Elbasvir/grazoprevir for patients with hepatitis C virus infection and inherited blood disorders: a phase III study. Hepatology. 66(3):736–745. https://doi.org/10.1002/hep.29139
15. Di Marco V, D'Ambrosio R, Bronte F, Saracco G, Lanza AG, Forni G, Poggiali E, Calvaruso V, Borsellino GZ, Cuccia L, Gerardi C, Maggio A, Madonia S, Fiorenza F, Salvo A, Caruso V, Russello MI, Fidone C, Davì A, Squadrito G, Aulenti G, Filosa A, Cianciulli P, Lai ME, Piga A, on behalf ITHACA (Italy for THAalassemia, hepatitis C Advances) Group (2016) Dual therapy with peg-interferon and ribavirin in thalassemia major patients with chronic HCV infection: Is there still an indication? Dig Liver Dis 48(6):650–655
16. Moon J, Hyland RH, Zhang F, Brainard DM, Lanzkron S, McHutchison JG, Sulkowski M (2017) Efficacy and safety of ledipasvir/ sofosbuvir for the treatment of chronic hepatitis c in persons with sickle cell disease. Clin Infect Dis 65(5):864–866. https://doi.org/10.1093/cid/cix441
17. Mehta R, Kabrawala M, Nandwani S, Desai P, Bhayani V, Patel S, Parekh V (2018) Safety and efficacy of sofosbuvir and daclatasvir for hepatitis C virus infection in patients with β-thalassemia major. J Clin Exp Hepatol 8(1):3–6. Available from:. https://doi.org/10.1016/j.jceh.2017.06.002

18. Nagral A, Sawant S, Malde P, Parikh P, Nagral N, Merchant R (2017) Experience with direct acting antivirals (DAA) agents in treatment of chronic hepatitis C virus (HCV) infection in patients of thalassemia major. J Clin Exp Hepatol 7:S14–S15. Available from:. https://doi.org/10.1016/j.jceh.2017.05.035
19. Ponti ML, Comitini F, Murgia D, Ganga R, Canu R, Dessì C, Foschini ML, Leoni GB, Morittu M, Perra M, Pilia MP, Casini MR, Zappu A, Origa R (2019) Impact of the direct-acting antiviral agents (DAAs) on chronic hepatitis C in Sardinian patients with transfusion-dependent Thalassemia major. Dig Liver Dis 51(4):561–567. Available from:. https://doi.org/10.1016/j.dld.2018.12.016
20. Nagral A, Jhaveri A, Sawant S, Parikh NS, Nagral N, Merchant R, Gandhi M (2019) Treatment of chronic hepatitis C infection with direct acting antivirals in adolescents with thalassemia major. Indian J Pediatr 86(2):148–153. https://doi.org/10.1007/s12098-018-2752-7

Publisher's Note