Original Article

Antiviral Treatment of Chronic Hepatitis C Infection among Children and Adolescents with Beta-Thalassemia Major

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Abstract

Background: Hepatitis C virus (HCV) was encountered as one of the most common infections transmitted through blood transfusion to thalassemic patients. After the discovery of new generations of antiviral drugs labeled direct-acting antiviral (DAA) drug since 2014, promising results were reported compared to older regimen of Peginterferon with or without ribavirin (RBV). **Objective:** The main objective of the study is to assess the hepatitis C viral status of multitransfused beta-thalassemia major patients and the sustained viral response rate to different modalities of therapy. **Materials and Methods:** A cross-sectional analytical study was conducted in Erbil Thalassemia Center. A sample of all children and adolescent (18 years or younger) patients of beta-thalassemia major with HCV antibody positive were reviewed according to the available medical records in the center. They were divided into two groups (first who received interferon ([IFN] ± RBV and second who received sofosbuvir (SOF) and daclatasvir [DCV]) for the aim of the study. **Results:** Among registered 695 patients with thalassemia major screened for HCV antibody, 659 children and adolescents were included and 186 were tested seropositive (28.22%), and they had been submitted to polymerase chain reaction analysis with HCV-RNA identified in 110 (59.13% of initially ELISA test positive). IFN-dependent therapy was given to 87 patients, while sofosbuvir and DCV for remaining 21 patients, sustained viral response was 100% among those received latter therapy with no reported relapse compared to former regimen of 44.3% sustained response and 6.33% relapse rate. **Conclusion:** DAA drug has a promising therapeutic result replacing the old therapy of IFN-RBV among thalassemic patients with 100% response rate in the study group.

Keywords: Adolescents, antiviral, children, hepatitis C, thalassemia major

Introduction

Beta-thalassemia major is a well-known disease requiring frequent blood transfusions, and hepatitis C virus (HCV) was encountered as one of the most common infections transmitted through giving blood. The chance of transmission of infection has been dramatically decreased since screening of blood donors have been started.[1]

Among patients who had received blood frequently before the 1990s, the rate of HCV infection was found to be increased to the number of pints of blood received and reached 80% in the adult age group.[2,3] Introduction of vaccine and educational health program lead to significant reduction in hepatitis B virus (HBV) infection.[4] It was estimated that around 350–400 million people in the world are chronic carriers of HBV, which represents approximately 7% of the total population, whereas infection with HCV is found in approximately 3% of the world population, which represents 160 million people.[5]

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In Eastern Mediterranean Region, the prevalence of HCV among the population was variable and range from 1% to 2.5% in most countries, with a high prevalence reported in Egypt (>10%), whereas in Iraq a range of 0.32%–7.1% had been reported. Iraq still regarded as a low endemic country for hepatitis B and C.[6,7]

The prevalence of HCV Infection among thalassemic patients range between 12% and 85%.[8] There are few reports in Iraq about the prevalence of infected patients, In Sulaimania (2009), 50% were polymerase chain reaction (PCR) positive for HCV, while it decreased to 26.4% reported by Raham *et al*. in Diyala.[9,10]

Genotype testing is widely used for children as well as in adults, genetic variability is a distinctive feature of HCV

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and viral sequences are currently classified into six different genotypes and more than 67 subtypes.[11] Few studies in Iraq involved genotyping with variable results, genotype 1 was the most common in a study conducted in Sulaimania (87.5%), while Khalid and Abdullah in Mosul revealed that genotype 4 is the most common subclass (94 of 100, 94%).[10,12]

The most important issue of hepatitis C infection is when to start medical therapy, which is still controversial. Those acutely infected with HCV (usually with no apparent-specific symptoms) are usually children who have normal alanine aminotransferase (ALT) values initially, and they are more likely than adults to recover from virus spontaneously.[13] Peginterferon (Schering), interferon (IFN)-α2b, and ribavirin (RBV) were approved by the Food and Drug Administration (FDA) for use in children older than 3 year of age with HCV hepatitis. Factors increase the response rate are younger age group, genotypes (1b, 2 and 3), RNA titer of <2 million copies/mL of blood, and viral response (PCR at weeks 4, 12, and even 24 of treatment). Due to hematological side effects of RBV, sometimes, the treatment will be discontinued and due to reported cases of spastic diplegia, IFN is not recommended for children below 3 year of age.[14,15]

The updated development in research and experimental trials started after 2011, and hence, the discovery of the new generations of antiviral drugs labeled direct-acting antiviral (DAA) drug established in 2014, such as sofosbuvir polymerase inhibitor (SBV, 2014), simeprevir protease inhibitor (SPV, 2014), and daclatasvir (DCV) NS5A inhibitor (NS5A, 2014), makes a huge impact in treatment of those patients with HCV infection. Then, other new drugs, such as beclabuvir, asunaprevir, ABT450/r + ombitasvir + dasabuvir, and ledipasvir, were newly approved by the FDA (European Medicines Agency) in 2014 as a combined single daily dose tablet (with sofosbuvir approved already by the FDA), with the brand name Harvoni.[4]

Children with HCV genotypes 2 and 3 are more likely to respond to the current treatments, so initiation of early treatment is advisable, while genotypes 1 and 4 are less likely to respond to such therapy.[13]

The aim of this study was to assess the hepatitis C viral status among multitransfused beta-thalassemia major patients and the sustained viral response rate (SVR) to different modalities of antiviral agents.

Materials and Methods

This cross-sectional analytical study was conducted in Erbil Thalassemia Center, Iraq. The center was first established in 1995 in Rizgary Hospital in Erbil City then became independent center at 2014 and located in Ankawa District. It receives all patients with hemoglobinpathies and 827 patients were registered including 695 with beta-thalassemia major.

A sample of 186 children and adolescents (18 years or younger) with beta-thalassemia major were hepatitis C virus positive. Patients with associated other infections such as hepatitis B or human immune deficiency virus, those with complicated cardiopulmonary manifestations or poor compliance to therapy, or did not complete treatment were excluded from the study.

All records of patients were reviewed and data (such as sociodemographic data, chelation therapy, splenectomy, hepatitis C genotypes, PCR virus load, doses of antiviral therapy, serum ferritin level, liver function test, and complete blood count) were entered for the analysis.

Automated platform, LIAISON® XL (DiaSorin S.p.A, Vercelli, Italy) anti-HCV screening assay, was used to detect positive immunoblotting results among those patients and positive results were confirmed by PCR testing and then genotyping.

Decision of treatment was made according to patient's age and updated guidelines.[16]

All patients with chronic hepatitis C infection without cirrhosis who received regular doses of IFN ± RBV (IFN-2b 1–1. 5 g/kg/week with or without RBV 15 mg/kg/day for 24 or 48 weeks) and those who received DAA (sofosbuvir and DCV, standard dose of 400 mg and 60 mg, respectively) were enrolled and divided into two groups according to mode of treatment for the aim of the study.

Later, their response will be classified into: early (EVR), sustained (SVR), and no response. PCR was done at 3 months (12 weeks) and at 6 months (24 weeks) to see Early Virological Response (EVR) and end treatment response (normal ALT plus a negative PCR). A Sustained Virological response (SVR) defined as undetectable HCV-RNA, 12 weeks or 24 weeks after treatment completion. Relapse is defined as undetectable HCV-RNA at the end of treatment but detectable HCV-RNA during follow-up.[16,17]

Statistical analysis

All data were tabulated and arranged in number, proportions, range (minimum, maximum), and mean ± standard deviation, and the association between variables was measured using Chi-square and independent *t*-test. $P \leq 0.05$ considered to be statistically significant.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study protocol and the subject information and consent form were reviewed and approved by a Local Ethics Committee (Medical college/Hawler Medical University). After registration in pediatric department, an official letter was introduced to thalassemia center in Erbil City regarding the study.

Results

Among registered 695 patients with thalassemia major screened for HCV antibody, 659 children and adolescents were included according to available data in the center and 186 were tested seropositive (28.22%), and they were submitted

to PCR analysis with HCV-RNA identified in 110 (59.13% of initially seropositive).

Those with PCR-positive results were exposed to antiviral therapy, two patients did not receive treatment properly and were excluded from the study and 108 patients were included. IFN ± RBV was given to 87 patients while sofosbuvir and DCV for the remaining 21 patients.

HCV genotype 3 was the most common type (43.6%) followed by 1 (35.5%), 4 (10.9%), mixed or non-typeable (7.3%), and finally 2 (2.7%) as demonstrated in Figure 1.

Table 1 demonstrate certain demographic, clinical, and biochemical data of thalassemia patients included in the study, male constitute largest portion and most of the patients received chelation therapy regularly. No treatment given to 78 patients, while remaining patients received antiviral medication as stated above.

Splenectomy was observed mainly in PCR-positive patients compared to negative group with significant $P = 0.021$. ALT level and platelet count were significantly higher among PCR-positive group compared to the other group [Table 2].

Among 110 patients of PCR-positive HCV, 108 received treatment with appropriate dose, 8 patients of 87 received IFN ± RBV did not have any response (no response category). Early viral response was obtained significantly higher in 18 of 21 (85.71%) exposed to new regimen therapy compared to 43 of 79 (49.4%) of opposite medication as demonstrated in Table 3.

Discussion

The rates of HCV-infected thalassemic patients in different countries range between 12% and 85%.[4] The prevalence had dropped since screening for blood donors had been established, here in Iraq, it was reported that 66.6% of thalassemic patients were infected at 1996.[18,19] Later, the prevalence started to decline and a large survey involved adults included 16 centers all over Iraq revealed that 13.5% of thalassemia patients had HCV infection at some point in their lives during the period from 2010 to 2015.[20] Recent studies in Diyala and Basra gives rate of 26.2% and 12.5%, respectively, verify the drop-in proportion of infected individuals with thalassemia major.[21,22] Countries like Pakistan and India published data of nearly same outcome in this study.[23,24] According to our data, 28.22% were seropositive and 59.13% of them were PCR-RNA positive which is still higher than what have been concluded in recent studies in Iraq[20,22] and nearby countries like Iran.[25] Turkey reported lowest rate of 4.4%.[4]

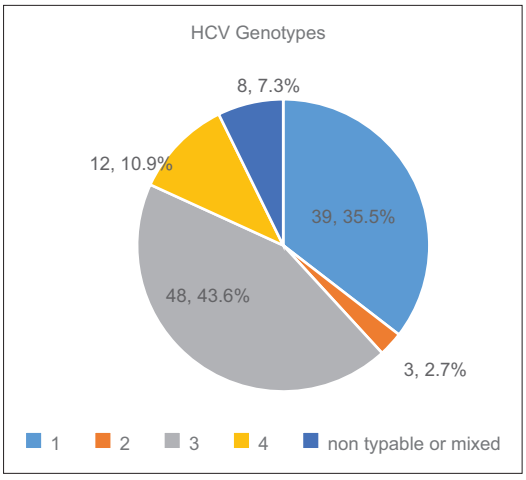

Figure 1: Genotyping of 110 patients with hepatitis C virus polymerase chain reaction-positive testing

Age at the time of conducting the study may affect many data, especially the prevalence as younger age groups may give lower prevalence rate. Male/female ratio was 67/43 among PCR-positive patients, but this was not significant as frequency of male registered in the center already was higher.

Genetic variability is a hallmark of HCV and changes according to geographical distribution; the Eastern Mediterranean Regional Office of the WHO published the collected reports in 2016 about the prevalence among population as well as HCV subtypes and revealed genotype 1 as the most common subtype reported in Iraq followed by 4 and 3.[26] Viral genotyping data in this study involved only those with thalassemia major indicate that type 3 as the most common one followed by type 1, and these results supported by figures recently published in Iran.[25] A total of 70 HCV infected frequently transfused patients with thalassemia major in Duhok were analyzed for genotyping using genotype-specific nested PCR, and surprisingly, the most frequent genotype detected was 4 (52.9%) followed by 3a (17.1%), 1b (12.9%).[27] Other variable reports showed

Table 1: Baseline characteristics of the study group (seropositive for hepatitis C virus)

Variables	Category	*n* (%)
Age	Mean: 13.85±3.72	186 (100)
	Median: 15	
Gender	Male	113 (60.8)
	Female	73 (39.2)
Weight	Mean: 35.47±11.1	186 (100)
	Median: 35	
Consanguinity	Yes	107 (57.5)
	No	79 (42.5)
Splenectomy	Yes	102 (54.8)
	No	84 (45.2)
Chelation Rx	Regular	163 (87.6)
	Irregular or didn't used	23 (12.4)
History of first-degree relative with thalassemia	Positive	132 (71.0)
	Negative	54 (29.0)
Antiviral therapy	No	78 (41.93)
	IFN ± RBV	87 (46.8)
	Sofosbuvir and DCV	21 (11.29)
Serum ferritin at screen time	4731.5±3787	186 (100)
Serum ALT at time of screen	105.19±73.1	186 (100)

ALT: Alanine aminotransferase, IFN: Interferon, RBV: Ribavirin, DCV: Daclatasvir

Table 2: Comparison of certain variables among polymerase chain reaction-positive and polymerase chain reaction-negative groups

Variables	PCR		*P*
	Positive (*n*=110)	Negative ((*n*=76)	
Age (mean)	13.88±3.83	13.80±3.57	0.887
Gender, *n* (%)			
Male	67 (60.9)	46 (60.5)	0.958
Female	43 (39.1)	30 (39.5)	
Splenectomy, *n* (%)			
Yes	68 (61.8)	34 (44.7)	0.021
No	42 (38.2)	42 (55.3)	
Frequency of blood transfusion per year	15.38 ± 4.48	15.53 ±4.65	0.817
Weight, mean±SD	36.49±11.57	34.00±10.28	0.133
ALT, mean±SD	112.70±75.87	74.58±51.14	0.017
AST, mean±SD	107.35±71.31	80.44±60.87	0.074
ALP, mean±SD	305.87±212.32	301.79±296.44	0.946
Serum ferritin, mean±SD	4910.07±4425.3	4480.12±2649.27	0.451
Hemoglobin, mean±SD	9.54±1.14	9.17±0.098	0.033
White blood cells, mean±SD	16,444.40±17,545.40	13,107.02±10,407.58	0.189
Platelet count, mean±SD	536.35±296.60	429.11±246.49	0.021

SD: Standard deviation, PCR: Polymerase chain reaction, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase

Table 3: Early viral response, relapse, and sustained viral response after receiving different antiviral agents

Variables	Antiviral treatment		*P*
	IFN±RBV (*n*=79)	Sofosbuvir and DCV (*n*=21)	
Response of Rx			
EVR*	43 (49.4)	18 (85.71)	0.009
No EVR	36 (41.4)	3 (14.9)	
Relapse			
No	74 (93.67)	21 (100)	0.58
Yes	5 (6.33)	0 (0)	
SVR			
Yes	35 (44.3)	21 (100)	<0.001
No	44 (55.7)	0 (0)	

*EVR of 3 months. SVR: Sustained virological response, EVR: Early virological response, IFN: Interferon, RBV: Ribavirin, DCV: Daclatasvir

dominant genotype 1 followed by type 3, but most of these studies lack a large sample size, and this may explain the dissimilarity.

Splenectomy despite not compared to noninfected groups in many studies, most of these papers demonstrate that nearly half of infected patients were splenectomized as observed in this study and was proved as risk factor for acquiring HCV infection.[25,28,29]

ALT was significantly higher among infected group with a mean value of (112.70 ± 75.87), and this could be a good predictor to distinguish infected patients with many studies have just about same mean value.[29]

Baseline serum ferritin level was surprisingly higher compared to previously published papers, and this could be explained by that older age groups in this study received iron-chelating therapy late or irregularly during their illness.[29,30]

Hemoglobin baseline level was not so important, as it was variable during phases of treatment due to frequent blood transfusion, but platelet count noticed to be significantly increased in hepatitis C PCR-positive group, and this may suggest its role as an inflammatory marker; however, it needs to be reviewed more as controversial reports did not conclude that.[30]

In this study, following EASL guidelines, SOF-DCV was among recommended regimen as an empirical therapy for chronic hepatitis c infection (Pangenotypic regimen) and was started in the center for those of 12 years or above, while younger age groups received old regimen (IFN ± RBV). EVR of 3 months was much higher and significant in the SOF-DCV patients (85.71%) compared to 49.4% of IFN ± RBV, and this strongly recommends the use of former mentioned antiviral therapy, but their efficacy still under trial among younger age groups.[30,31]

Many studies done in Iraq regarding response to therapy and biochemical markers was the main indicator of response as in a study conducted on thalassemic patients in Baghdad reviewed effect of IFN ± RBV revealed 10 patients out of 21 patients (47%) showed complete response (which defined as normalization of ALT levels which usually occurs rapidly, generally within 2 months of initiation of treatment).[30] A detailed review in Greece about SVR of infected patients with hemoglobinopathies demonstrates 13% failed to respond and 40% relapse rate with IFN based therapy which is still higher than our data of 6.33% with IFN ± RBV therapy.[32]

HCV-DAAs were first licensed in Europe in 2014, and first three drugs (sofosbuvir, simeprevir, and DCV) had a SVR of

60%–100% in infected adults and is considered as affective therapy for all genotypes in noncirrhotic chronic HCV infection.[32]

SVR among nonthalassemic HCV-positive patients had improved dramatically since 1986 with the introduction of 6-month IFN monotherapy from 6% to 55% after 12 months of IFN ± RBV combination therapy at 2002 and reached nearly 100% with IFN-free DAA introduction.[33]

SVR in this study reached 100% with DAA new therapy group compared to 44.3% of the other group, unfortunately, comparable results regarding new regimen on infected thalassemic patients were limited due to older age group trials (>18 year) and most published papers studied SVR of genotypes as response varied according to the type and drugs.

Responses of different genotypes restricted by small sample size in this study, especially of SOF-DCV therapy as 2 or less have genotypes 2, 4, or mixed.

Limitation of the study was lack of histological data, as most patients did not exposed to liver biopsy and hence Hepatitis Activity Index grading and score was not applied, ended with empirical treatment regardless the histological features. Very few studies involved thalassemic patients even among adults make it hard to compare our results with previous articles.

Conclusion

DAA has a promising therapeutic result replacing the old therapy of IFN ± RBV among thalassemic patients with 100% SVR in the study group. These results need to be supported by further studies with larger sample size, especially for the new therapy of SOF-RBV and other DAA trials including younger age groups.

Recommendations

These results need to be supported by further studies with larger sample size, especially for the new therapy of SOF-RBV in children of younger age groups.

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Conflicts of interest

There are no conflicts of interest.

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