ORIGINAL ARTICLE

EFFECTIVENESS AND SAFETY OF DIRECT ACTING ANTIVIRAL AGENTS IN THALASSAEMIC PATIENTS WITH CHRONIC HEPATITIS C

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Background: Pakistan has the highest prevalence of B-Thalassemia major in children and Chronic Hepatitis C (HCV) infection is a common transfusion transmitted infection. After the emergence of new generations of Antiviral drugs labelled as Direct Acting Antivirals (DAAs), substantial eradication of HCV has been reported as 90–95% with fewer side effects as compared to older regimen of Peginterferon with or without Ribavirin. The main objective of this study was to assess the Rapid virological response (RVR) at 4th week, End of treatment response (ETR) at 12th week and sustained viral response (SVR) at 24th week achieved by using direct acting antiviral and to assess their safety. **Methods:** Retrospective descriptive study was conducted from July 2018 to July 2020 at National Institute of Child Health. All β-thalassemia major paediatric patients with HCV infection and age between 3–14 years were included. Demographic data, liver function test, HCV PCR, and response of antiviral therapy was recorded and analyzed. Safety was determined by adverse effects reported in records and efficacy was documented by clearance of HCV-RNA to see ETR and SVR. **Results:** Total 21 patients were treated. Mean age was 7.67±3yr and 12 (57%) were male. Mean weight was 19.3±3.2kg. RVR and ETR was achieved in all (100%) and SVR was achieved in 20/21 (95%) patients. Headache in 2(9.5%) and generalized body ache was found in 1 (4.25%) patient. **Conclusion:** Combined Sofosbuvir and Daclatasvir were found to be effective and safe for treating HCV in Thalassaemia Major Children.

Keywords: Sofosbuvir; Daclatasvir; Thalassemia; Hepatitis C

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INTRODUCTION

B-Thalassemia is the major inherited disorder globally with Pakistan having the highest prevalence of children with this problem.[1] Every year approximately 5000–9000 children are born with β-thalassemia and around 100,000 transfusion-dependent β-thalassemia patients are there in our country.[2] These patients are on higher risk of transfusion transmitted infections including Hepatitis C virus, Hepatitis B virus (HBV) and Human immunodeficiency virus (HIV).[3] Globally reported prevalence of Hepatitis C infection (HCV) in β-thalassemia patients ranges between 12% and 85% and in Pakistan, the reported HCV infection rate in these patients is 44% (35–52%).[4,5] This infection can be prevented by proper screening of donor blood. Our country has resource limited settings and unfortunately due to financial constraints, the screening procedure is not of standard quality and the responsible cause for this happening is use of rapid testing kits with poor sensitivity.[6] Iron overload and simultaneous chronic HCV hepatitis increases the risk of progression of fibrosis of liver causing severe liver disease.[7] Previously the recommended treatment for children, interferon and Ribavirin had limited efficacy with significant side effects and increased frequency of haematological complications in β-thalassemia major patients.[8] After the emergence of new generations of Antiviral drugs labelled as Direct Acting Antivirals (DAAs) since 2013, substantial eradication of HCV has been reported as 90–95% with fewer side effects.[9] Mehta R *et al* used DAAs (Sofosbuvir and Daclatasvir) in 10–18 year old β-thalassemia patients and found favourable response of treatment.[10] In 2017, Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved direct-acting antiviral (DAA) for the treatment of chronic hepatitis for 12–17 years old. Various DAAs in different combinations are used in children and adolescents including sofosbuvir and ledipasvir in aged 6-17 years old, sofosbuvir and ribavirin for adolescents, ombitasvir, paritaprevir, and ritonavir for adolescents and sofosbuvir plus daclatasvir for children. The available results indicated good efficacy and safety.[11] Hashmi M A and Cheema H A used Sofosbuvir and Ribavirin in children and found these drugs as highly effective and safe.[12] Sofosbuvir (SOF) was licensed by the Drug Regulatory Authority of Pakistan in 2014 and Daclatasvir (DAC) became available in 2018 in Pakistan.[13] DAAs were used in β-thalassemia

major adult patients with advanced liver disease and no significant adverse events were found and there was no drug-drug interaction reported between DAAS (Sofosbuvir, Daclatasvir) and commonly used iron chelating agents (Deferasirox, deferoxamine and deferiprone) in β-thalassemia patients.[14] We aimed to assess the Rapid virological response (RVR) at 4 weeks, end of treatment response (ETR) at 12 weeks and sustained virological response (SVR) at 24 weeks achieved by using these direct acting antiviral (Sofosbuvir and Daclatasvir) for chronic hepatitis C in β-Thalassemia Major Patients and to assess the safety of these drugs.

MATERIAL AND METHODS

Retrospective descriptive study was conducted from July 2018 to July 2020 at National Institute of Child Health Karachi after taking approval from institutional ethical committee. β-thalassemia major paediatric patients who were receiving regular blood transfusions and had anti HCV antibody positive were included. The age range was from 3–14 years. Patients who had concomitant Hepatitis B surface antigen positive and or HIV antibodies positive were excluded. Patients, who had features of advanced liver disease like ascites and prolonged prothrombin time, were excluded. AST Platelets ratio Index (APRI) was calculated and patients having APRI ratio >1 and previously treated patients were also excluded. Demographic data, clinical examination and investigations including CBC, Aspartate Aminotransferase (AST), Alanine Aminotransferase levels (ALT), serum ferritin, serum creatinine, hepatitis C viral PCR (qualitative and quantitative) and response of antiviral therapy was analyzed. CBC, ALT, AST, Ferritin and creatinine before treatment were recorded. HCV PCR readings qualitative as well as quantitative were recorded which included before start of treatment and thereafter only qualitative was done and recorded at 4th week, 12th week and at 24th week (12 weeks after completion of treatment). Qualitative HCV PCR not detected at 4th week of treatment was labelled as Rapid Virological Response (RVR) achieved, HCV PCR not detected at 12th week of treatment was labelled as End of Treatment Response (ETR) achieved and HCV PCR not detected at 12th week after completion of treatment was labelled as Sustained Virological Response (SVR) achieved. Sofosbuvir 200 mg/day for patients weighing 17–35 kg and Daclatasvir 30 mg/day for patients weighing 17–35 kg for 12 weeks were used. Safety was determined by recording symptoms and signs developed during treatment period and by recording follow up investigations including CBC, ALT, AST, Ferritin and creatinine at 4th week and 12th week of treatment. Efficacy was determined by clearance of HCV-RNA to see rapid virological response e(RVR), End of treatment response (ETR) and sustained virological response (SVR).

Data was analyzed by program SPSS version 24. Descriptive statistics were calculated for qualitative and quantitative variables. Qualitative variables included gender, hepatomegaly, splenomegaly, HCV genotypes, virological response and side effects were calculated and presented as frequency and percentages. Quantitative variables included age, weight, platelet count and HCV PCR titer were presented as mean and standard deviation. Age stratification was done as <6 years and ≥6 years as previously treatment was recommended for >6 years old. Normality testing using Shapiro-Wilk test was done for baseline and after the treatment biochemical parameters including ALT, AST, Ferritin and serum creatinine. Data was not normally distributed so non-parametric test for paired samples, Wilcoxon Signed-Rank Test was applied for comparison of baseline and after treatment biochemical parameters and were presented as median/interquartile range. *p*-value <0.05 was taken as significant.

RESULTS

Total 25 β-thalassemia major patients had anti HCV antibody positive and HCV PCR was detected in 21 patients. Twenty-one patients were treated with DAAS during the study period. Mean age was 7.67± 3 year and 12 (57%) were male. Mean weight was 19.3±3.2 kg, hepatomegaly in 13 (62%), and splenomegaly in 8 (38%) was noted. Genotype was done in 14 patients (67%). Out of them genotype 3 was in 11(78%) and genotype 1 was in 3 patients (22%). The mean viral load was $3.9X10^6 \pm 6.5X10^6$ IU/ml. Rapid virological response and end of treatment response was achieved in all the patients. Sustained virological response was achieved in 20/21 (95%) of patients only one patient who had detected HCV RNA at 24 weeks after achieving ETR. The genotype of that patient was type 3 and after re-detection of HCV PCR, genotype was repeated and that repeated genotype showed type 1 indicating re-infection rather relapse. Follow up ALT, AST and serum ferritin were significantly decreased after treatment with significant *p*-value <0.01. There was no significant difference in serum creatinine level with *p*-value= 0.126 and mean platelets count was 265±104/µl as shown in Table-3. Two patients (9.5%) reported headache in last month of treatment and one patient (4.25%) reported generalized body ache which were treated with oral paracetamol symptomatically. No other significant sign or symptoms developed during treatment and there was

no significant change noted in investigational parameters including CBC and serum creatinine.

Table-1: Baseline demographic and clinical characteristics of beta thalassemia major patients with hepatitis-c virus infection

Parameters		
Age (n=21)	<6years, n (%)	09 (43%)
	≥6years, n (%)	12 (57%)
Gender (n=21)	Male, n (%)	12 (57%)
	Female, n (%)	09 (43%)
Treatment-naive, n=21 n (%)		21 (100%)
Weight <35Kg, n=21 n (%)		21 (100%)
Hepatomegaly, n=21 n (%)		13/21 (62%)
Splenomegaly, n=21 n (%)		09/21 (38%)
Genotype (n=14)	Type 3, n (%)	11/14 (78%)
	Type 1, n (%)	03/14 (22%)
HCV RNA Titer, mean±sd		3.9X106±6.5X106IU/ml

Table-2: Virological Response (n=21)

Response: HCV RNA not detected	n (%)
Rapid Virological response (RVR)	21 (100%)
End of Treatment Response (ETR)	21 (100%)
Sustained Virological Response (SVR)	20 (95%)

Table-3: Baseline and post-treatment laboratory tests of patients with beta thalassemia major (n=21)

Parameters	Baseline Median (IQR)	At 12th week Median (IQR)	*p*-value
Haemoglobin (gm/dl)	8.4 (1)	9 (1)	0.031
ALT (IU/ml)	155 (187)	44 (43)	<0.01
AST (IU/ml)	113 (263)	56 (81)	<0.01
Ferritin (ng/ml)	3040 (1157)	2339 (1172)	<0.01
Creatinine (mg/dl)	0.43±0.13	0.40±0.23	0.126

DISCUSSION

Beta Thalassemia major patients require lifelong blood transfusions, hence susceptible to transmission of chronic HCV infection.[15] HCV infection and iron overload are independent factors for progression of liver fibrosis and development of cirrhosis; therefore, it is double trouble and must be diagnosed and managed timely.[16] In our study mean age of patients was 7.67±3 year that was lower as compared to previously reported studies from Pakistan. Mainly there are adults' studies and in paediatrics Hashmi MA *et al* reported mean age of 10years and Alvi MA *et al* reported 14± 2.5years.[12,17,18] Male to female ratio in our study was 1.3, male were predominant same as reported by Hashmi *et al* 1.7 times male and Alvi MA *et al* 1.6 times male, even higher ratio of males in their studies as compared to our study.[12,17] Nine patients in our study were less than 6 years of age and youngest one was 3 years old. Schwarz *et al* used Sofosbuvir based DAAS in 3 to <6 years of age.[19] Sana Kamal *et al* compared the course of severity of liver disease in chronic hepatitis C with and without β-thalassemia and found that spontaneous resolution is lower and progression of fibrosis is accelerated in chronic hepatitis C having β-thalassemia emphasizing earlier treatment is required for better outcome.[20] Genotype 3 was most common genotype found in our study and that is similar to both Pakistani paediatric studies reported highest percentage of genotype 3 in their studies.[12,17] Before 2017 the protocol treatment of HCV infection in children (3 year and older) had been a combination of pegylated interferon and Ribavirin with efficacy of 59% for all genotypes. This therapy had significant side effects like need for weekly injections, fever, anorexia, nausea, headache, anaemia, Ribavirin induced haemolysis and Interferon induced bone marrow suppression.[21] Newer treatments with DAAs have revolutionized the treatment of HCV infection in children by showing increased rates of SVR and limited side effects.[21,22] Much of the studies have been conducted on adult population for safety and efficacy of DAAs but the data on paediatric population with β-thalassemia major is still scarce. In our study, 21 Thalassemia Major Patients with HCV infection were treated, RVR achieved in all (100%), ETR achieved in all (100%) and SVR was achieved in 20 patients except one (95%). Hashmi M A et reported 100% ETR and 97.14% SVR in a paediatric study from Pakistan having 5 Thalassemia patients and Alvi M A reported 100% ETR and SVR in 21 adolescent Thalassemia patients. Nagral *et al* reported 89% patients achieved SVR at 3 months post completion of treatment with DAAs with no side effects in adolescent Thalassemia patients.[23] Wirth et al in his cohort study which comprised of 52 non thalassemia adolescents showed that DAAs based combination of SBV+RBV resulted in SVR of 100% in genotype 2 and 97% in genotype 3 at 12 weeks.[24] Our study is the first study having younger children with thalassemia treated with DAAs in our country. The results of our study were highly promising and encouraging. Repeated HCV PCR at 24th week in that one patient who did not achieve SVR showed re infection with another genotype as previously that was type 3 and on repeat it was found to be genotype 1. Although there is high response rate of treatment but it does not enhance immunity so in patients with persistent risk factors have the chances of re-infection with same or another genotype.[25]

In our study, the baseline ALT was higher in our patients (mean value 128±68 IU/ml) and it was decreased after completion of treatment (64±38 IU/ml) with significant p-value. Similar results were reported from study done in Iraq and Pakistani paediatric studies.[26,12,17] There were no significant haematological side effects noted. There was no significant decrease in haemoglobin level and platelets counts and there was no increase in serum

creatinine. Padhi S *et al* used Sofosbuvir and Daclatasvir in adult dosage to 5–14 year old children of Chronic Hepatitis C with β-Thalassemia Major and reported SVR in all patients and found these drugs safe and effective without any haematological derangement.[27] Similar findings were noted by Zamani F et al who reported effectiveness of SOF and DAC for HCV infection in β-Thalassemia Major patients without any haematological adverse effects.[28] Serum ferritin level was done in our patients to see baseline iron overload and it was also repeated after completion of treatment. It was significantly decreased after treatment and similar result were reported in previous study from Pakistan.[17] In our study 2 patients had headache and one had generalized body ache that was treated symptomatically no other serious side effect was noted and these were also similar with the previous reported studies.[12,17]

Limitations in our study were the retrospective review of our patients. The present outcome of our study has further emphasized that Sofosbuvir based therapy can be safely used in HCV treatment in children with β-thalassemia major patients who are on chelating therapy but further prospective studies should be conducted in these children having chronic hepatitis C with Thalassemia Major patients.

CONCLUSION

Combined Sofosbuvir and Daclatasvir were found to be effective and safe for treating HCV in Thalassemia Major Children. We recommend the continued screening and treatment of these children. Suggestions can be given that there is dire need of reform of our blood banks and we need to improve our screening strategy by using highly sensitive and PCR based assay for safe transfusion and prevention of such transfusion transmitted infections

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AUTHORS' CONTRIBUTION

AP: Study design, conceptualization, data analysis, data interpretation. AAM: Literature search, write-up, drafting of content. SHA, WH: Helped in data collection, since they work in haematology and infectious disease department. NH, NAM: Data analysis, questionare design.

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