Original article

Ribavirin free direct-acting antivirals in adolescents with hepatitis C and thalassemia

Muhammad Arshad Alvi[1], Huma Arshad Cheema[2], Anjum Saeed[3], Sara Batool[4]

[1]Assistant Professor, [2]Professor, [3]Associate Professor, [4]Senior Registrar, Department of Pediatrics Gastroenterology & Hepatology Children's Hospital Lahore Pakistan.

Correspondence to: Dr Muhammad Arshad Alvi, Assistant Professor, Pediatric Gastroenterology, Hepatology & Nutrition, The Children's Hospital & the Institute of child health, Lahore, Pakistan. Email: alviarsh@gmail.com

ABSTRACT

Background: Recently introduced antivirals (ribavirin free direct-acting antivirals) are now recommended in pediatric age group above 12 years of age but are not yet extensively studied in thalassemic patients with hepatitis C infection. This study aims to study the safety and efficacy of newer ribavirin-free direct acting antivirals in thalassemic children with hepatitis C.

Patients and Methods: All thalassemic patients with hepatitis C virus (HCV) infection fulfilling the inclusion criteria were recruited consecutively. Ribavirin free direct-acting antivirals (DAA) were started according to genotypes. Virological response was assessed at baseline, four, twelve and twenty-four weeks. Data regarding safety and efficacy of DAA in these children were collected and analyzed by SPSS.

Results: Twenty-one patients met the criteria for enrolment in the study. Sustained virological response (SVR) was seen in all patients (100%) at 24 weeks. Regarding adverse events in patients receiving daclatasavir plus sofosbuvir, nausea was seen in 33% followed by increased blood transfusion requirements in 22%, fatigue in 16%, headache in 11% and pancytopenia in one patient (5%). Patients receiving velpatasavir and sofosbuvir therapy, none of side effects were noted.

Conclusion: Ribavirin free DAAs are highly effective in thalassemic patients with hepatitis C and minimal adverse effects are observed especially in children receiving daclatasavir and sofosbuvir.

Keywords:
Thalassemia, HCV, DAAs, Blood Transfusion, Daclatasavir, Sofosbuvir

INTRODUCTION

Hepatitis C (HCV) infection is a major co-morbid condition in thalassemia patients and around 12-85% patients are carrier of hepatitis C around the world.[1] Due to preventive measures like mandatory screening for HCV, new cases of hepatitis C in Europe have significantly reduced. But transfusions-related HCV infection is still quite prevalent in developing countries like Pakistan.[2] The major contributing factors in HCV transmission in these countries are the use of non-sterile injections, improper or inadequate blood screening and use of paid blood from professional donors. Liver is one of the predilected site for damage caused by hepatitis C and iron cumulatively increasing the risk of hepatic cirrhosis in patients with thalassemia.[3-5] The prevalence of hepatic cirrhosis in thalassaemic patients with HCV is documented in many studies with frequency of 10-20%.[6-9] Due to availability of very effective iron chelation therapy, the survival of these patients has significantly increased but at the cost of liver-related mortality and morbidity.[10] Therefore, it is desirable to treat hepatitis C virus infection in these patients. In the past the only treatment option was PEG-interferon and ribavirin for the treatment of HCV infection with low sustained virological response (SVR) of 25-72 % with these drugs.[11-13] There were lot of reservations with this combination like ribavirin induced hemolysis, several contraindications, poor tolerance, and variable efficacy.[14] With advances in clinical research, newer antiviral drugs have been introduced for the management of HCV infection in adults. Sofosbuvir (polymerase Inhibitor) was the prototype followed by Simeprevir and Daclatasvir with a great relief to patients and treating physicians. These newer direct acting antivirals (DAAs) have changed the treatment of HCV as these are found to be very effective (SVR > 90%) and safe in adults. According to recent guidelines, these new regimens can be used in thalassemic patients as sole treatment without ribavarin.[15] However, data regarding use of these medications in pediatric age group is still limited and physicians are still inclined to use the conventional treatment until enough evidence-based treatment options regarding safety and efficacy of newer agents as sole treatment in pediatric age population is approved. A lot of trials are underway because of recently FDA approval for children above 12 years of age.[16-19] This study aims to

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evaluate the safety and efficacy of ribavirin-free direct acting antivirals in thalassemic children with hepatitis C infection.

PATIENTS AND METHODS

This was a prospective observational study in an outpatient setting of the Children's Hospital and the Institute of Child Health, Lahore. The adolescent patients between ages of 12 and 18 years with the diagnosis of Thalassemia and Hepatitis C infection were recruited from June 2017 till May 2018. Children with HIV or hepatitis B virus co-infection, children previously treated with interferon-based regimen or direct acting antivirals and children with cirrhosis were excluded. Informed written consent was taken by parents/guardians before the start of the study after explaining all the aims and objectives of the study.

Procedure: Each patient underwent baseline complete blood count, liver and renal function tests and serum ferritin levels. HCV viral load and genotype were determined using reverse transcription polymerase chain reaction assay (Qiagen/Rotor gene) and genotype amplisense kit respectively at immunology laboratory of Children's hospital, Lahore. Virological response (HCV RNA) was assessed at baseline, week-four of treatment, end-of treatment and twelve weeks after cessation of the treatment. All patients with genotype 3 and un-typable genotypes received fixed dose combination of sofosbuvir (SOF) 400 mg and daclatasavir (DCV) 30 mg daily for twelve weeks and SOF 400 mg plus velpatasavir (VEL) 100 mg for genotype 1 and genotype 4. No change was made in the treatment of the patients receiving iron-chelating agent (desferoxamine/ deferiprone). Data regarding side effects and treatment response was collected at baseline, four, twelve, and twenty-four weeks (twelve weeks after completion of therapy). Blood transfusion requirements (ml/month) was collected at each clinical visit. Previous blood transfusion requirement (ml/month) before starting treatment was also asked and compared with blood transfusion requirement during the treatment in each patient. In addition, patients were asked to visit any time in the hospital or to call by phone for reporting any side effect. The effectiveness of the treatment was assessed based upon the achievement of Rapid Virological Response (HCV RNA < 15 IU/mL) at week 4 of the treatment, sustained virological response, (SVR) (HCV RNA < 15 IU/mL), twelve weeks after cessation of the treatment, and end of treatment response (ETR) (HCV RNA < 15 IU/mL) at the end of treatment. Virological relapse was defined as reappearance of Hepatitis C (HCV RNA > 15 IU/mL) in patient who achieved ETR. Occurrence of adverse event was noted as reported by the patients or on the basis of abnormal laboratory findings. Data analysis was performed and reported as mean±standard deviation (SD), median or proportions (percentages) as appropriate for the level of measurement and distribution of the variables. Wilcoxon Rank test was performed to compare pre-treatment and post-treatment laboratory variables. Statistical analysis was performed using SPSS version 20.

RESULTS

Twenty-one patients with transfusion dependent B-thalassemia who developed hepatitis C infection were included. Among twenty-one patients, fifteen patients of Genotype 3 and three patients of un-typable genotype were treated with fixed doses of SOF (400 mg) and DCV (30 mg) daily for 12 weeks. Thirteen patients (62%) were male and 8 patients (38%) were female. Mean age of the patients was 14.30 ±2.5 years, other parameters like durations of illness, mean ALT and ferritin level are summarized in Table 1. Two patients of genotype 1 and one patient of genotype 4 were treated with SOF (400 mg) and VEL (100mg) for 12 weeks. Table 2 depicts direct antivirals according to different genotypes. In 18 patients who received DCV plus SOF rapid virological response (RVR) was observed in 16 patients (89%). Two patients were unable to achieve RVR, one patient was noncompliant and second child had high baseline viral load (14,31383copies/ml). However, end of treatment response (ETR) was 100% (18/18). Virological relapse was not seen in any patient and hence rate of sustained

Table 1: Demographic and baseline characteristics children with HCV and thalassemia (N=21).

Characteristics	Results
Male	13 (62%)
Female	08 (38%)
Age (years)	14±2.5
Duration of illness (days)	198±107
History of splenectomy	5 (23.8%)
Serum ALT (IU/l)	115±55.3
Serum ferritin (µg/ml)	5465±2517

Table 2: SVR for various direct acting antiviral regimen according to hepatitis C genotypes (N=21)

Genotype	No. of patients	DAA regimen	Treatment duration	SVR
1	2	Velpatasavir + Sofosbuvir	12 weeks	100%
4	1	Velpatasavir + Sofosbuvir	12 weeks	100%
3	15	Daclatasavir + Sofosbuvir	12 weeks	100%
Untypeable	3	Daclatasavir + Sofosbuvir	12 weeks	100%

virological response was 100%. In four (22%) children, blood transfusion requirement increased but only one patient required discontinuation of treatment after one month due to significantly increased transfusion requirements (increased from 700 ml/month to 1600 ml/month) and severe pancytopenia, so changed to alternative regimen (velpatasavir plus sofosbuvir) with improvement of pancytopenia and blood transfusion requirements. There was significant decrease in serum ferritin level from 5465±2517 to 3093±1049 (p- value = 0.000) and alanine amino transferase (p-value= 0.000) after completion of the antiviral treatment as shown in Fig 1. Three patients received velpatasavir and sofosbuvir, RVR was 100% (n=3/3), and same was ETR and SVR as shown in Table 2. None of children required increased blood transfusion requirement, rather in two children transfusion requirements decreased by one week. Regarding other adverse events, no fatalities were reported during the period of the study. Majority of patients had mild side effects, nausea in 6/18 (33%) patients, fatigue and weakness was seen in 3/18 (16%) patients, increase transfusion requirement in 4/18 (22%) patients, headache in 2/18 (11%) patients, whereas one (5%) child developed severe pancytopenia. While in patients receiving velpatasavir and sofosbuvir therapy, no side effects were noted.

DISCUSSION

Hepatitis C in thalassemic patients is known to cause high mortality but there are very few studies in the pediatric population and this study attempts to contribute local data on use of DAA in children with thalassemia. The study employed sofosbuvir/daclatasvir in genotype 3 and un-typeable genotypes and sofosbuvir/velpatasavir in genotype 1 and 4. The results showed that this combination is highly effective in the treatment of children with hepatitis C and thalassemia, though some children developed minimal adverse effects especially those receiving sofosbuvir and daclatasavir. Sustained virological response and end of treatment response was 100% in patients receiving daclatasavir and sofosbuvir in this study. This is similar to study done by Mehta and coworkers on ten pediatric patients of thalassemia with hepatitis C genotype 3.[20] In their study sustained virological response, rapid virological response and end of treatment response was100%. However, they used adult dose of DCV 60mg with SOF 400mg. Similar results were achieved in present study with half dose of DCV 30 mg plus full dose of SOF 400mg, as pharmacokinetic studies demonstrated that levels of SOF in adolescents were within the pre-defined pharmacokinetic equivalence when compared with adults from Phase 2 and 3 studies.[21] However there are no pharmacokinetic studies on daclatasavir dose in pediatrics. In present study rapid virological response was 89% in patients receiving daclatasavir and sofosbuvir but end of treatment response was 100%. Only Two children could not achieve rapid virological response, one remained non complaint in first month of treatment and the other had very high viral load (1431383copies/ml). Almost similar results were published by Mehta and colleagues in which two out of 10 patients did not achieve rapid virological response (RVR), both of patients had high viral load. El-Sayed and coauthors also reported 100% SVR by using daclatasavir and sofosbuvir in adult dose on adolescent age group.[22] Their study was done on non-thalassemic patients. A study done by Yakoot and group on non-thalasemic patients of pediatric age group, by using sofosbuvir plus daclatasavir in adult doses in hepatitis C genotype 4, showed 96.7% sustained virological response. Only one child in their study did not achieve sustained virological response and lost to follow up after one month of treatment, however he did achieve rapid virological response.[23] In present study, children receiving velpatasavir and sofosbuvir, rapid virological response, end of treatment response and sustained virological response was 100%. However only three children received velpatsavir and sofosbuvir. Regarding liver enzymes, alanine aminotransferase (ALT) showed significant improvement after treatment of hepatitis C, same results were shown by other authors.[25] However in this study ALT was still above the normal value in some patients. This could be due to concomitant high iron overload. Regarding blood transfusion, 22% patients in

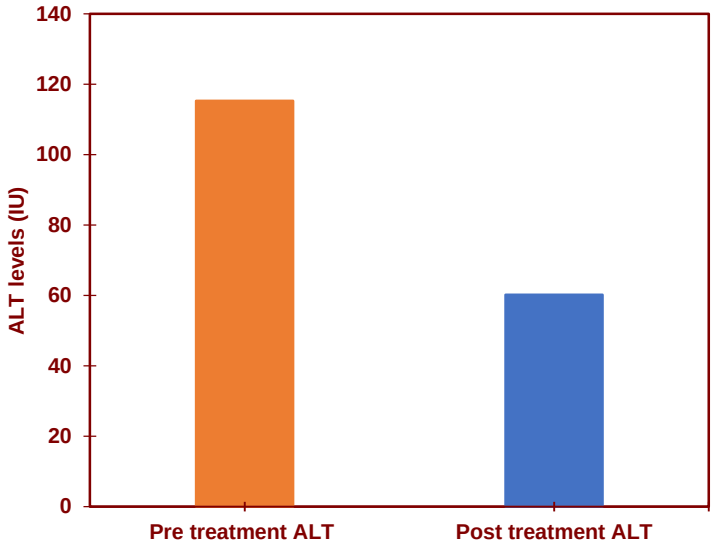

Figure 1: Trend of alanine aminotransferase (ALT in IU, vertical axis) pre and post treatment of HCV in 21 thalassemic children (horizontal axis)

this study had increased transfusion requirements despite of ribavirin free treatment. Onali and group documented similar results with 8.7% of their patients receiving ribavirin-free direct antivirals developing anemia.[24] Authors could not find any other study in the indexed English literature done on non-thalassemic pediatric patients reporting anemia. This could be because of paucity of studies done on pediatric age group using daclatasavir and sofosbuvir. Study done by Mehta and coauthors on 10 thalassemic patients using sofosbuvir and daclatasavir with 7 patients in pediatric age range showed no evidence of anemia. In present study one child receiving daclatasavir plus ribavirin developed pancytopenia. No other study could be traced reporting this side effect. Again, this may be due to only fewer studies performed on thalassemic patients. Other adverse events reported in this study were not severe enough to require discontinuation of therapy. Three children who received velpatsavir and sofosbuvir in this study did not show any side effects, rather in two of these children blood transfusion requirement improved. More studies with larger sample are needed to validate this observation and to confirm safety of velpatsavir and sofosbuvir in thalassemic children with hepatitis C.

CONCLUSION

This prospective study showed that ribavirin-free DAAs are safe and effective in adolescent aged thalassemic children with hepatitis C.

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