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Original Research Article

Effectiveness of directly acting oral antivirals in treatment of chronic HCV infection in children - experience from a tertiary care institute in southern India

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ABSTRACT

Background: Worldwide, an estimated 71 million people are chronically infected with HCV, of which an estimated 2.1- 5.0 million are children aged ≤15 years. Children with chronic HCV infection have fewer treatment options than adults. Very few reports are available on HCV infection, treatment strategies and its outcome particularly in pediatric population. In this background, we evaluated the effectiveness and safety of Sofosbuvir/Ledipasvir in treating HCV infection in children.
Methods: In this retrospective study, a total of 33 children with HCV positive status, 12 cases (children above 12 years of age) were selected for treatment. HCV-RNA quantitative assay, genotyping was carried out. Children above 12 years with HCV genotype 1 were treated with tablet ledipasvir-sofosbuvir (90/400 mg) orally once a day as morning dose for 12 weeks. Children with genotype 3 were treated with sofosbuvir 400 mg and weight based ribavirin for 24 weeks. Viral load was repeated after 12 weeks of completion of treatment with antivirals for sustained virological response (SVR 12).
Results: Out of the 12 patients 11 patients had genotype 1 (5/11 had subtype-1a and 6/11 had subtype-1b) infection and only 1 patient has genotype 3 (subtype-3a). All of them attained SVR at the end of 12 weeks. The regimen was well tolerated and there were no side effects noted by the children and their caretakers. Drug compliance and the palatability of the drugs were good.
Conclusions: Ledipasvir-sofosbuvir combination was highly effective at treating children with chronic HCV genotype 1 infection. The availability of an all oral, direct-acting antiviral regimen for paediatric population with chronic HCV would improve care for patients who currently have limited treatment options.

Keywords: Hepatitis C virus, Ledipasvir, Sofosbuvir, Sustained virological response

INTRODUCTION

Hepatitis-C virus (HCV) has a major health impact in the global scenario. Worldwide, an estimated 71 million people are chronically infected with HCV, of which an estimated 2.1- 5.0 million are children aged ≤15 years. In India, the prevalence of HCV infection in children is estimated at 3.6% in those aged 1-9 years. A report published by WHO in 2017 states the prevalence of HCV in pediatric age group was 13.2 (11.5–21.2) million

children.[1,2] In children, the primary route of HCV infection is perinatal transmission. The rate of perinatal transmission of HCV infection is approximately 5%, although rates are higher in cases co-infected with Human Immunodeficiency virus (HIV) or high Hepatitis-C viral loads (>6 log IU/mL).[3,4] More than 10 regimens have been licensed for treating HCV in adults. Each of these regimens can achieve sustain virological response (SVR) >90% with only 12 weeks oral treatment. The current standard of care for HCV infections in adults includes several all-oral regimens comprising direct-acting antivirals (DAAs) that specifically target HCV. DAAs are highly effective and have a favourable safety profile. Therefore, almost all adult patients have been able to achieve HCV eradication.[5]

However, children with chronic HCV infection have fewer treatment options than adults. Until recently, the standard of care for chronic HCV pediatric infections was interferon or peginterferon and ribavirin therapy for 24 or 48 weeks, a regimen that requires subcutaneous injections and is associated with major side effects, including growth impairment. Moreover, the SVR for HCV genotype 1 and 4 are 64% (treatment-naïve patients), but 50% in cases with high viral load and about 89% in genotype 2 and 3. The FDA approved the usage of drugs, sofosbuvir/ledipasvir in adolescence (>12 years) and study report revealed that the drug is highly safe and effective in children aged 6-11years.[6,7] Very few reports are available on HCV infection, treatment strategies and its outcome particularly in pediatric population.

Hence, the objective of the study was to evaluate the effectiveness and safety of antiviral drugs, Sofosbuvir/Ledipasvir in treating HCV infection in children.

METHODS

This retrospective study was carried out in Department of Gastroenterology, Institute of Child Health and Hospital for children, during the period of October 2018 to May 2020. The inclusion criteria were children who had completed 12 years of age with HCV positivity; HCV related chronic liver disease. Exclusion criteria were children less than 12 years of age; co-existing HBV infection, HIV co-infection; cases who had previously treated with interferon/ribavirin. In a total of 33 children with HCV positive status, 12 cases (children above 12 years of age) were selected for treatment with directly acting antivirals based on the HCV genotypes as per the EASL guidelines.8 HCV-RNA quantitative assay and genotyping was carried out using RT-PCR.

Complete blood test including complete blood count, liver function test, renal function test, prothrombin time and International Normalized Ratio (PT/INR), ultrasound abdomen and oesophago-gastro deuodenoscopy were carried out and results were recorded. HBsAg and HIV co-infection were ruled out. Diagnosis of cirrhosis was made by clinical, laboratory and radiological methods.

Children above 12 years with HCV genotype 1 were treated with tablet ledipasvir-sofosbuvir (90/400 mg) orally once a day as morning dose for 12 weeks. Children with genotype 3 were treated with sofosbuvir 400 mg and weight based ribavirin for 24 weeks. Patients were monitored for drug compliance and side effects were analysed with biochemical and haematological parameters. Viral load was repeated after 12 weeks of completion of treatment with antivirals for sustained virological response (SVR 12). Data were analyzed using SPSS 15.0 statistical software.

RESULTS

In a total of 21 HCV positive cases (who were not included in the study as per EASL guidelines), eight patients were <12 years of age and were placed on follow-up; 13 patients had viral load below undetectable levels. Of the 12 patients who were included in the study, eight were male (66.7%) and four were female (33.3%). The baseline characteristics were given in Table 1.

Table 1: Baseline characteristics.

Variables	Range (min-max)	n (%)
Male		8 (66.7)
Female		4 (33.3)
		Mean±SD
Haemoglobin (gm/dL)	8.9 - 14.1	11.52±1.7
Total Count (Cells/cubic mm)	1700-18900	8975±4997
Platelet (lakhs/µl)	7000-5.53 lakhs	2.59±1.7
INR	0.9-1.2	1.05±0.1
Serum creatinine (mg/dL)	0.3-0.9	0.5±0.2
Serum bilirubin (Total) (mg/dL)	0.5-2	0.94±0.5
Serum albumin (g/dL)	3.6-4.2	3.9±0.2
AST (IU/L)	40-181	71.7±46.5
ALT (IU/L)	22-151	77.25±33.5
HCV-RNA (IU/L)	5170-10000000	2326822.7± 3213239.5

Out of the 12 patients who were eligible for therapy, six patients had completed treatment for Acute lymphocytic leukemia (ALL), one for Acute myeloid leukemia (AML), two were Thalassemic and one child was diagnosed with aplastic anaemia. The remaining two children had renal diseases in the form of nephrotic syndrome and Atypical hemolytic uremic syndrome (aHUS) (Table 2).

Almost all of the children had previous history of blood products transfusion during the course of their illness. None of the children had features of cirrhosis. No previous

history of treatment with interferon/oral antivirals was noted in the group.

Table 2: Co-morbidities among the study participants (N=12).

Co-morbidities	No. of patients with co-morbidities
Acute lymphocytic leukemia (ALL)	6
Acute myeloid leukemia (AML)	1
Thalassemia	2
Aplastic anemia	1
Chronic kidney diseae (CKD)	1
Nephrotic syndrome	1

Table 3: Distribution of HCV genotypes among the study participants (N=12).

HCV Genotype	Subtype	Male	Female	Total
Genotype 1		8 (100%)	3 (75%)	11 (91.7%)
	1a	3 (37.5%)	2 (50%)	5 (41.7%)
	1b	5 (62.5%)	1 (25%)	6 (50%)
Genotype 2				-
	2a	-	-	-
Genotype 3		-	1 (25%)	1 (8.3%)
	3a	-	1 (25%)	1 (8.3%)
	3b	-	-	-
Total		**8**	**4**	**12**

Out of the 12 patients 11 patients had genotype 1 (5/11 had subtype-1a and 6/11 had subtype-1b) infection and only 1 patient has genotype 3 (subtype-3a) (Table 3). None of the children had HBV/HIV co infection. All of them attained SVR at the end of 12 weeks. The regimen was well tolerated and there were no side effects noted by the children and their caretakers. Drug compliance and the palatability of the drugs were good. Adherence to the treatment was good and no patients were lost in the follow-up. We treated all the study participants using DAA regimens, and a sustained virological response (SVR) was achieved in all patients.

DISCUSSION

Approximately 120 to 180 million individuals throughout the world are infected with hepatitis C virus.9 The paediatric population contributes to about 11 million who were under 15 years of age. Infections due to HCV genotypes vary geographically. Genotype 1 (46.2% of HCV infections) is the most widespread worldwide and is responsible for most infections in developed countries, which is well correlated with our study report. The second most frequent is genotype 3 (30.1% of HCV infections), which is often found in South Asia, Europe and the US among drug users infected with HCV.[10]

Studies regarding treatment of chronic hepatitis C in children are limited. Current standard treatment of chronic HCV infection in children was pegylated interferon with ribavirin over a period of 48 weeks. The disadvantage of this therapy was high incidence of side effects like cytopenias along with poor SVR. Direct acting antivirals came as a boon in the management of chronic HCV infection. Adult patients treated with DAAs have far superior SVR than their counterparts treated with Peg IFN/Ribavirin. So, there has been a paradigm shift in the treatment of chronic HCV in adults from IFN to DAAs.

Other challenges that the interferon based regimen needed longer duration of treatment (24-48 weeks). This also needed close follow up. A long list of side effects was well known with the Interferon and ribavirin that causes poor compliance or necessitate dose modification.

Recently the use of DAAs in children was scanty and various trials have been conducted in the paediatric age group in DAAs. In 2017, the European Medicines Agency (EMA) and FDA approved the use of ledipasvir/sofosbuvir (LDV/ SOF) 90 mg/400 mg OD to treat adolescents (ages 12–17 or weight >35 kg) with genotypes 1, 4, 5 and 6 for 12 weeks.[11]

FDA approved weight based sofosbuvir plus ribavirin for treatment-naive and interferon-experienced (±ribavirin) children aged ≥ 3 years with genotype 2 or 3, without cirrhosis or with compensated cirrhosis (Child-Pugh A). A 12-week course is recommended for pediatric patients without cirrhosis, and 24 weeks is recommended for those with compensated cirrhosis.[12]

DAAs are classified into several categories: NS3/4A protease inhibitors, nucleotide and non-nucleotide inhibitors of NS5B polymerase, and NS5A inhibitors. The development of new combinations of DAAs is based on that at least 2 drugs are needed to achieve the treatment goal of obtaining high virological response rates (>90%) without development of resistance.[5]

Eradication of HCV in children offers plenty of benefits to children, such as a reduction in disease progression, emotional strain and prevention of transmission. Based on these benefits, antiviral therapy seems to be preferred for HCV-infected children, regardless of liver fibrosis and the liver function impairment.

CONCLUSION

Ledipasvir-sofosbuvir combination was highly effective at treating children with chronic HCV genotype 1 infection. The availability of an all oral, direct-acting antiviral regimen for paediatric population with chronic HCV would improve care for patients who currently have limited treatment options. The expansion of HCV

treatment options to include all oral DAA regimens for children and adolescents will improve the accessibility of treatment worldwide. Direct acting antivirals are a boon in the treatment of chronic HCV infection in children with a good sustained virological response in a cost effective manner with negligible side effects.

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