ORIGINAL ARTICLE

Effectiveness and Safety of Sofosbuvir in Treatment-*Näive* Children with Hepatitis C Infection

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Abstract

Objective: To determine the effectiveness and safety of Sofosbuvir and Ribavirin combination in treatment-*näive* children with HCV infection.

Study Design: An experimental study.

Place and Duration of Study: Gastroentrology, Hepatology Department, The Children's Hospital and The Institute of Child Health, Lahore, from January to December 2016.

Methodology: HCV PCR positive treatment-*näive* patients, 5 to 18 years of age, were enrolled by consecutive non-probability sampling. Clinical features and investigations including complete blood count, bilirubin, ALT, PT and HCV genotyping were done. All patients were started on Sofosbuvir 400 mg once daily and Ribavirin 10-15 mg/kg/day. Patients were followed on 4-weekly basis. PCR was done after 4 weeks; if positive then again at 12 weeks. End of treatment and 12 weeks post treatment PCR was done in all patients. Total duration of therapy was 24 weeks. Computer program SPSS version 20 was used for data analysis.

Results: A total of 35 patients with mean age of 10.24 ±2.80 years, including 22 boys (62.86%), and 13 girls (37.14%) were included. The most common HCV genotype was genotype 3 encountered in 27 (77.15%), followed by genotype 1 in 6 (17.14%), while 2 (5.71%) patients were untypable. Thirty (85.71%) patients achieved rapid virological response while the rest 5 (14.28%) had early virological response. End-of-treatment PCR was negative in all patients. SVR was achieved by 34 (97.14%) patients. The treatment was well tolerated. Headache was observed in 8 (22.86%) patients, which improved spontaneously.

Conclusion: Sofosbuvir and Ribavirin combination is highly effective in HCV genotypes 1 and 3 with no major undesirable short-term side effects.

Key Words: *Hepatitis C virus. Sofosbuvir. Ribavirin. Treatment-näive. Children.*

INTRODUCTION

Hepatitis C is prevalent in world's population to endemic proportions with an estimated overall disease burden of 170 million. It is a hepatotropic virus which causes continuous inflammation and tissue damage with long-term complications of cirrhosis and hepatocellular carcinoma.[1] The prevalence of chronic HCV infection in American children is 0.17%, in those between 6-11 years of age, and 0.39% in those between 12-19 years of age.[2] Prevalence of HCV infection in Bangladesh is 0.6%,[3] while the estimated prevalence in Pakistani children is 0.58%.[4]

The standard of treatment for HCV infection in children (3-year and older) is a combination of pegylated interferon α-2a or α-2b with Ribavirin.[5] The overall efficacy of this combination regimen is between 53-65% and depends upon the viral genotype study, overall efficacy in all genotypes being 59%.[6] Most patients experience at least one adverse event. Serious side effects mandating discontinuation of therapy are encountered in only 4% of patients. Constitutional symptoms, fever, anorexia, fatigue, nausea, headache etc. are attributed to Interferon.[7] Bone marrow suppression due to interferon is seen in one-third of the patients. Less common side effects include irritability, depression and suicidal intent.[8] Thyroid dysfunction is also a known complication of interferon and Ribavirin combination regimen.[9] Ribavirin is commonly associated with hemolytic anemia, which is a result of oxidative damage caused by drug metabolites. It usually responds to dose reduction.[10]

The drawbacks of Interferon and Ribavirin therapy include the need for weekly injections, poor efficacy against HCV genotypes 1 and 4 and side effects as already mentioned. New agents are being studied which inhibit HCV at different steps of replication. Sofosbuvir is a very promising agent which inhibits viral replication by binding to NS5B RNA dependent RNA polymerase and has high sustained virological response rates against HCV genotypes 1,2,3,4 and 6.[11] It was approved by FDA for the treatment of chronic HCV infection in December 2013 and was first licensed in Pakistan by the Drug Regulatory Authority of Pakistan in November 2014. The overall efficacy in all genotypes has been reported as

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high as 93.85%. The medicine is well tolerated even in patients with cirrhosis; although headache and asthenia might experienced.[12]

This study was planned to determine the effectiveness and safety of Sofosbuvir in combination with Ribavirin in Hepatitis C infection in children above five years of age, as data in paediatric age group is lacking.

METHODOLOGY

This open labeled un-controlled trial / experimental study was carried out in the Department of Paediatric Gastroenterology, Hepatology, The Children's Hospital and The Institute of Child Health, Lahore, Pakistan from January to December 2016. After approval from Hospital ethical committee and explaining the purpose and procedure of the study, informed written consent was taken from parents/guardians. All the out patients, in-patients as well as patients referred from other departments of the hospital and other hospitals were considered. Patients of either gender aged between five and 18 years, who were HCV PCR positive and had not received any HCV-related treatment, were enrolled by consecutive non-probability sampling. Patients with severe renal impairment (GFR <30 mL/min/1.73 m^2) or end-stage renal disease (ESRD), decompensated liver disease (APRI score >1.5) post-liver transplant and the previously treated patients were excluded.

Patients with active malignancy, receiving chemotherapy, were excluded from the study; while those in remission having completed chemotherapy were included in the study.

Sample size (n) was calculated using WHO sample size calculator keeping confidence level (1 - α) 95%, absolute precision (d) 8% and effectiveness of Sofosbuvir and Ribavirin combination 93.85%.[12] The formula:

$$n = Z_1^2 \frac{\alpha}{s} \frac{P\,(1 - P)}{d^2}$$

was used for calculating the sample size which was 35.

Data was collected on an especially designed proforma at the first contact, including age and gender. Stigmata of chronic liver disease (CLD), i.e. clubbing, palmar erythema, spider *nevi*, hepatosplenomegaly and ascites was clinically noted. Complete blood count, bilirubin, ALT, PT and HCV genotyping was done. All patients were started on Sofosbuvir 400 mg once daily and Ribavirin 10-15 mg/kg/day in single or two divided doses. Patients were followed in outdoor on 4-weekly basis.

History about any adverse effects was taken at each visit. Complete blood count, bilirubin, ALT, PT and APTT was done on every follow-up visit. PCR was done after four weeks; if positive then it was repeated at 12 weeks. End-of-treatment PCR was done in all patients. Total duration of therapy was 24 weeks. PCR was also repeated 12 weeks after the completion of therapy.

Effectiveness was determined for each genotype in terms of clearance of HCV RNA determined by real time qualitative PCR. Rapid Virological Response (RVR) was defined as negative PCR at four weeks of treatment. Early Virological Response (EVR) was defined as PCR posiive at four weeks of treatment but negative at 12 weeks of treatment. Sustained Virological Response (SVR) at 12 weeks post-treatment was the endpoint of study and was defined as HCV PCR negative after 12 weeks of completion of treatment duration of 24 weeks. Safety was defined as lack of serious side effect requiring cessation of therapy.

Computer program SPSS version 20 was used for data analysis. Descriptive statistics was calculated for both qualitative and quantitative variables. Qualitative variables included gender, HCV genotypes, CLD stigmata, virological response and side effects; presented as frequency and percentages. Quantitative variables included age, hemoglobin TLC, platelet count, bilirubin, ALT, PT were subjected to normality testing using Shapiro-Wilk test. Variables with normal distribution were presented as mean + standard deviation, while non-parametric variables were presented as median/interquartile range. Wilcoxon Signed-Rank Test was used to compare the pre-treatment and post-treatment ALT, while paired sample t-test was used for comparing pre-treatment and post-treatment hemoglobin. P-value <0.05 was considered significant.

RESULTS

The total number of patients included in the study were 35, having mean age of 10.24 ±2.80 years with 22 boys (62.86%) and 13 (37.14%) girls. Mean APRI score was 0.58 ±0.33 with a range of 0.10 to 1.32. The most common HCV genotype was genotype 3 encountered in 27 (77.15%), followed by genotype 1 seen in 6 (17.14%), while 2 (5.71%) patients were untypable. Most of the patients had pre-existing hematological disorders including thalassemia major in 5 (14.28%) patients, acute lymphoblastic leukemia and non-Hodgkin lymphoma in 2 (5.71%) patients each, and von-Villibrand disease and Hodgkin disease in 1 (2.85%) patient each. Rhabdomyosarcoma and Wilson disease were also present in 1 (2.85%) patient each.

Most frequent mode of transmission of HCV was blood products transfusion seen in 15 (42.86%) followed by perinatal transmission that was documented in 7 (20.00%) patients. History of previous surgery was present in 4 (11.43) patients, while 1 (2.85%) patient had history of tattooing. No risk factor could be identified in 8 (22.86%) patients.

Virological response in current trial was highly encouraging as all patients achieved virological remission by 12 weeks of treatment (Table I). Majority of the patients, i.e. 30 (85.71%), achieved rapid virological

Table I: Virological response by genotypes (n=35).

	Genotype 1 Frequency (%)	Genotype 3 Frequency (%)	Untypable Frequency (%)
Number of patients	6/35 (17.14%)	27/35 (77.15%)	2/35 (5.71%)
Virological response	6/6 (100%)	27/27 (100%)	2/2 (100%)
Rapid virological response	5/6 (83.33%)	23/27 (85.19%)	2/2 (100%)
Early virological response	1/6 (16.67%)	4/27 (14.81%)	0/2 (0.00%)
Sustained virological response	6/6 (100%)	26/27 (96.29%)	2/2 (100%)

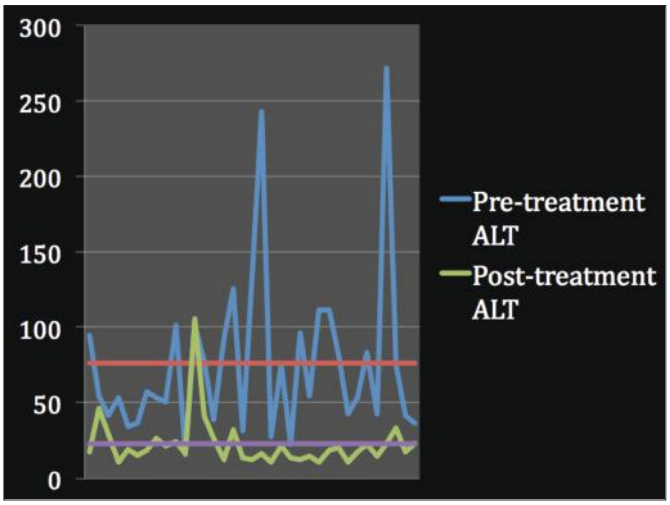

Figure 1: Improvement in liver enzymes after treatment.

response with undetectable viral RNA by 4 weeks of treatment, while rest 5 (14.29%) were negative by 12 weeks of treatment. All the patients were PCR negative for HCV RNA at the end of treatment. SVR 12 weeks post-treatment was achieved by 34 (97.14%) patients.

Mean hemoglobin before the start of treatment was 11.49 ±1.92 g/dL, while post-treatment hemoglobin was 11.11 ±1.65 g/dL. The drop in hemoglobin level was statistically insignificant (p = 0.43). Patients also showed a significant improvement in liver enzymes. Pre-treatment ALT was raised in 25 (71.43%) patients, while it normalized in most of the patients with only 2 (5.71%) patients having elevated ALT at the end of treatment (Figure 1). Distribution of both pre-treatment and post-treatment ALT was abnormal (p < 0.001). Median pretreatment ALT was 55 IU/ml with interquartile range of 55, while median post-treatment ALT was 19 IU/ml interquartile range of 11. The improvement of ALT after treatment was highly significant (p < 0.001).

The treatment was well tolerated in most patients and none of the patients had serious side effects. Headache was observed in 8 (22.86%) patients which gradually improved by 12 to 16 weeks of therapy in most of the patients except one who was developmentally delayed and had severe headache, requiring cessation of therapy at 8 weeks. However, viral clearance at 4 weeks of therapy was achieved in this patient and PCR at 24 weeks was also negative. Constipation was observed in one (2.85%) patient that required mild laxative.

DISCUSSION

Hepatitis C is an emerging problem in paediatric age group. In present study, mean age at presentation was about 10 years while there was roughly 2:1 male predominance. In another local study, mean age at presentation was 18 years with a female preponderance; contrary to the present study.[13] However, in a recent meta-analysis, male were found 1.7 times more frequently infected than females; in close proximity to the results of present study.[14]

Repeated blood product transfusions and perinatal transmission were identified as the most common etiological factors in the present study. Less common factors were surgery and tattooing. There is a close correlation in these results and contemporary literature.[14] However, in most of the developed countries, improved and effective donor screening programs have remarkably reduced the blood borne transmission of HCV infection. As a result, perinatal transmission is the major etiologic factor responsible for HCV transmission in most developed countries.[15] Contrary is the situation in most developing countries where blood borne transmission is still the major route of HCV transmission, as is evidenced by the current study also.

Interferon-based regimens have been the standard of care for treatment of HCV. However, directly acting antiviral drugs have added a new dimension to the treatment of HCV. Data is rapidly emerging to suggest the efficacy and safety of different combination regimens in both treatment-*näive* and treatment-failure cases. As a result, the interferon-based regimens are rapidly being replaced. These agents include Sofosbuvir, Ledipasvir, Daclatasavir, Dasabuvir, Ombitasvir and Paritaprevir, which are under trial in different combinations. However, available data on their efficacy and side effects is mainly limited to adult population only.[16] These agents have shown to be highly safe and effective in high risk groups of patients such as end-stage kidney disease and liver cirrhosis.[17]

Present study constitutes the pioneer work on directly acting antiviral agents in children and adolescents in the country. Only treatment-*näive* patients with HCV infection were included in the study. The patients were found to have genotypes 3 and 1 with few cases untypable. The results of our study were highly encouraging. All patients achieved virological response and most of the patients achieved rapid virological response. All patients were PCR negative at 12 weeks and at end of treatment. SVR was also very high, i.e 97%.

In comparison with the standard Pegylated Interferon α-2a and Ribavirin combination regimen, this efficacy is much higher. In a study done in adolescent population, virological response was achieved in 86.3% patients treated with Pegylated Interferon α-2a and Ribavirin.[13]

Data about the effectiveness of Sofosbuvir and Ribavirin combination in paediatric age group is very much deficient. Overall SVR in HCV genotypes 1 and 3 in adult population was 94.3% in the study by Mehta.[18] This high response rate very much endorses the result of present study.

Open labeled uncontrolled trials are under way in other parts of the world to evaluate the effectiveness of newer drugs in paediatric population. These include a trial of Sofosbuvir and Ribavirin combination; and another trial of Sofosbuvir and Ledipasvir combination in children and adolescents in United States of America. Conclusion of these trials will further help in establishing the role of newer regimens in paediatric HCV infection.[19,20]

Although scarcity of published paediatric data on the subject in study makes comparison difficult; however, it is evident from the results of present study that Sofosbuvir-based, interferon-free regimens are going to be the future face of paediatric HCV treatment. High response in HCV genotype 1, which was traditionally considered the poor prognostic genotype, makes it the game changer. Much more work is needed in paediatric population in order to establish the long-term safety as well as risk of recurrence.

CONCLUSION

Sofosbuvir in combination with Ribavirin is highly effective in children infected with HCV genotypes 1 and 3, without major undesirable short-term side effects.

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