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Efficacy of Sofosbuvir and Ribavirin in Children Presenting with Hepatitis C at Tertiary Care Hospital, Faisalabad

Naginal Shahzadi, Naureen Kanwal Satti, Huma Arshad, Nadeem Hashmat

ABSTRACT

Objectives: To assess efficacy, safety, and outcome of combination of Sofosbuvir and Ribavirin in various genotypes, in children with hepatitis C infection.

Study design and setting: It was a quasi-experimental study, conducted at the Gastroenterology and Hepatology Department, Children Hospital Faisalabad, from August 2017 to August 2021.

Methodology: 50 confirmed cases of HCV infection aged 5 to 18 years, were given an oral dose of Sofosbuvir and Ribavirin daily for 12 weeks. PCR was assessed at 4 weeks (for Rapid Viral Response (RVR)) and repeated at 8 weeks and 12 weeks (for Early Viral Response (EVR)) and again 12 weeks after the completion of therapy for Sustained Viral Response (SVR)). Primary outcome was the number who achieved an SVR at 12 weeks (SVR12) after completion of treatment with a viral load below quantitation level.

Results: Genotype 3 was found in 80% , type 1 in 6% , type 2 in 4% and 10% were untypeable. All children were PCR positive at presentation; 96% became PCR negative at 4 weeks (RVR), while 100 percent were negative at 8 weeks, 12 weeks (EVR), and SVR 12 weeks after completion of 12 week course was 100%.

Conclusion: Although majority of patients were Genotype 3, 12 week course of Sofosbuvir and Ribavirin of hepatitis C-infected children was highly effective, with 100 percent PCR-negative cases at 8 weeks and 12 weeks with only minor side effects, and, SVR of 100% twelve weeks after completion of therapy.

Keywords: Chronic Hepatitis C, Children, Antiviral, Sofosbuvir, Ribavirin

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INTRODUCTION:

Hepatitis C (Hep C) infection is a global health burden in children as well as adults. It is estimated that 70 million people, or 1% of the population, are infected with hepatitis C worldwide [1]. In Pakistan 6.5% population is afflicted with Hep C with prevalence in children of 1.6%.[2] Chronic Hep C virus infection is the most common cause of liver transplantation globally and its importance is signified by 2016 WHO strategy to reduce Hep C infection by 90% by 2030.[3]

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Hep C virus has 6 genotypes. The most common worldwide is type 1 with a prevalence rate of 49% globally, followed by genotypes 3, 4, and 2 with prevalence rates of 17.9%, 16.8%, and 11% respectively. The rest of the genotypes account for less than 5%.4 On the other hand, the most common genotypes prevalent in Pakistan are 3 and 3 b, followed by 1a, 2a, and untypeable.[5]

The routes of spread of hepatitis C in Pakistan include reuse of syringes, surgical procedures, dental extractions, blood transfusions, perinatal transmission, and reuse of instruments at barbershops. Chronic disorders requiring repeated blood component transfusions have an alarmingly high prevalence of Hep C; a meta-analysis done on 5789 beta-thalassemics revealed a prevalence of 36.21%6

Diagnosis of Hep C virus requires PCR to confirm on Serology Positive patients. Genotyping is done to further categorise into one of the 6 genotypes.

The importance of treating hepatitis C disease in childhood cannot be overemphasised due to its impact on halting progression to chronic liver disease in later years.

Until 2017, pegylated interferons and ribavirin were the only approved treatments for children with hepatitis-C. This

treatment regime has several drawbacks, including duration of treatment, compliance, and parenteral use for a longer duration than Direct Antiviral Agents (DDA). DAAs were approved for children above 12 years of age by the FDA in 2017.Recently, the FDA has approved the use of Sofosbuvir and Velpatasvir in children 6 years and older and weighing at least 17 kilograms with any of the genotypes of hepatitis C.[7] At the time of writing of this account, WHO has already recommended conditional use (due to very low certainty of evidence) of combination of DAAs from 3-5 years of age.8 Sofosbuvir and Ribavirin is the first combination approved for use in children. Limited local data is available regarding its efficacy and safety in children. A study done in The Children's Hospital Lahore showed excellent results of Sofosbuvir and Ribavirin combination in children in genotypes 1 and 3 with sustained virologic response of 97%.[9] Recent treatment recommendations in all children older than 03 years are use of interferon free directly acting antiviral regimens. First line combinations are Glecaprevir and pibrentasvir for 08 weeks in children 12 years and older and Sofosbuvir and Velpatasvir Ribavirin for 12 weeks in children 03 years and older. These combinations have good virological response across genotypes. All patients older than 03 years having positive HCV detection by PCR should be treated regardless of initial viral load, genotype and liver biochemistry.[10]

The introduction of DAAs has dramatically changed the treatment outcome of hepatitis C in children. In Pakistan Genotype 3 is the predominant genotype, seen in the large majority of patients. Data on the use of Sofosbuvir and Ribavirin in adults is available in Pakistan, but there is limited data on its use in children. The available studies, globally and locally, however have shown excellent results with a combination of Ribavirin and Sofosbuvir.?'[11] Both drugs are used in combination and are safe in children with fewer side effects. Standard recommendation for genotype 3 is a regimen of 24 weeks, but since RVR and EVR are excellent in genotype 3 patients in studies done to date, we assume that if we give a regimen of 12 weeks only, this effect will be maintained in SVR 12 as well. Therefore we planned to do a 12 week treatment study. This may increase confidence in retaining Ribavirin in regimens used to treat Hep C in children and increase its acceptability because of short duration.

METHODOLOGY:

A Quasi-experimental study was conducted from August 2017 to August 2021. The research was carried out in the Gastroenterology and Hepatology Department of the Children Hospital and Institute of Child Health, Faisalabad, to investigate the efficacy, safety, outcome, and complications profile of treatment with Sofosbuvir and Ribavirin for 12 weeks in Hepatitis-C confirmed cases.

The study was approved by the Ethical Review Board of The Children Hospital and Institute of Child Health, Faisalabad bearing ERC number "33" dated 10-11-2020. Informed written consent was taken from parents or guardians of all children prior to enrolment in this study. Eligibility criteria for patients to be enrolled for the study included; age above 6 years (> 5 completed years) to 15 years, the evidence of chronic HCV infection with any genotype (positive Qualitative PCR) and no prior treatment at any centre for HCV. Patients who had decompensated liver disease, co-infection with Hepatitis A, B or HIV, end stage renal disease or any history of psychiatric illness, were excluded from the study. Children who had previously received any treatment for HCV infection were also excluded from the study.

Patients were enrolled using the Consecutive Sampling technique. Openepi.com Sample Size Calculator was used to calculate the sample size keeping confidence interval 95%, absolute precision 5%, and anticipated efficacy (sustained virologic response at 12 weeks after completion of therapy) 97%.[11] Therefore Effect Size was 97. Total sample size thus calculated was 10 by Kelsy, 8 by Fleiss and 12 by Fleiss with CC. Our sample size however was 50 cases, well above the calculated numbers.

A detailed proforma was filled out, which recorded a detailed history, all clinical features of chronic liver disease, extrahepatic manifestations, disease severity, and the exclusion of other causes. Other causes of liver disease were ruled out using biochemical tests and imaging. To rule out concomitant infection, baseline tests including hepatic viral markers for HBV, HCV, HAV, and HIV were performed. Data on HCV transmission routes, risk factors, lab work, and previous treatment received by patients were collected.

All enrolled patients were followed up at 04 weekly intervals. The history of new symptoms and clinical signs, as well as any side effects related to the medication and the disease itself, were recorded at four-week intervals during the course of treatment. If advanced liver disease was suspected, CT scans, MRIs, and endoscopies were performed to rule out the disease and its complications.

Patients were given Sofosbuvir 400 mg once daily and Ribavirin at a dose of 10-15 mg per kg twice daily for 12 weeks irrespective of the genotype. All children were closely monitored, and a 4-week follow-up was performed, which included a detailed history of clinical signs and symptoms after treatment, as well as lab work. A CBC was performed weekly to assess low Hb levels, as well as LFTs, serum albumin, INR, PT, and APTT. PCR was assessed at 8 weeks and repeated at 12 weeks. Finally, PCR was done 12 weeks after the treatment finished. The primary outcome was efficacy, which was defined as the number of patients who achieved a sustained viral response 12 weeks after the medication stopped (SVR12), which was the treatment's end point and defined as a negative PCR or a viral load less

than the quantitation level. Safety was defined as no or minimal nonspecific side effects during a 12-week treatment period that did not necessitate drug discontinuation.

The data was analysed with SPSS 20.0, and the study's findings were subjected to qualitative and quantitative assessments. A statistically significant P-value was defined as less than 0.05. Demographics, disease presentations, reaction to therapies, changes in lab values, compliance, and complications of disease or treatment failure were all assessed quantitatively and qualitatively.

RESULTS:

In total, 50 children of both genders participated in the study. The group consisted of 38 males (76%) and 12 females (24 %). The male-to-female ratio was 3.2:1. The median age was 7.2 years. The most common genotype was type 3, which was found in 80% of patients, followed by type 1, which was found in 6% of patients and type 2 in 4% of patients. In 10% of patients, genotype could not be determined and were labelled untypable (Figure: 1).

At the time of the presentation, all of the children tested positive for PCR. 56 % cases were admitted from Outpatient Department and 44% were referred from Hematology and Oncology ward. Blood transfusion was the most common mode of Hep C transmission, accounting for the vast majority of cases. Children with thalassemia made up 74% of the cases. Bleeding and platelet function disorders accounted for 12% of all cases; 2% had previous abdominal surgery, and 2% had perinatal transmission, 4% of cases were in remission from leukaemia and the aetiology could not be determined in remaining 6% of cases.

A staggering 86% of cases had comorbidities. 80% had chronic blood transfusion requirements, including thalassemia, leukaemia, lymphomas, bleeding disorders and platelet disorders, which still speaks volumes about the importance of routine blood screening before transfusion.

ALT was raised in 97% of cases, and the mean ALT at the beginning of treatment was 67, while post treatment ALT became normal in all the cases. Mean ALT post treatment at 12 weeks was 17.6 and the difference after treatment was significant ($p < 0.001$). Another significant finding was a drop in haemoglobin from a mean of 11.6± 1.42 at the start of treatment to 10.10 ±1.45 ($p < 0.002$).

At 4 weeks, 96% of patients were PCR negative, and 100% were negative at 12 weeks of treatment. SVR (Negative PCR at 12 weeks after stopping treatment) was also 100% (Figure: 2). Poor appetite was observed in 76.6 percent of cases, weakness and lethargy in 64% of cases, vomiting in 16% of cases, and headache and abdominal pain in 56% and 66% of cases, respectively.

DISCUSSION:

The success of DAAs in adults with hepatitis C has opened up new possibilities for paediatric hepatitis C treatment. For

Figure 1: HCV Genotypes

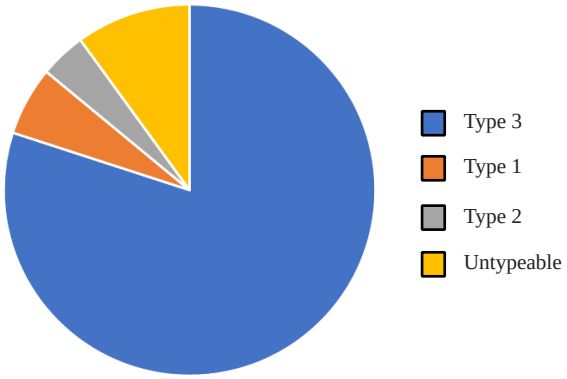
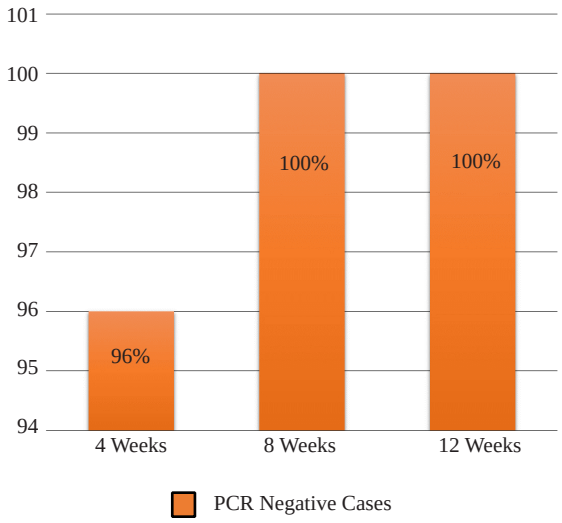


Figure:2 Percentage of PCR Negative cases at 4,8 and 12 weeks



children over age six, they are more powerful and safer than conventional therapy methods. In children, Ribavirin and Sofusbuvir have been used in a few trials, and have resulted in high SVR post therapy with minimal adverse effects since the introduction of DAAs. Trials have shown a 98% effectiveness rate as compared to 60 to 70% efficacy with interferons. The traditional interferon treatment regimen has a number of side effects, including effects on children's growth and low success rates in genotypes 1 and 4, which have been successfully treated with DAAs [12,13].

The average age in our sample was 7.2 ± 0.5 years, with a male to female ratio of nearly 3:1. According to a recent assessment of the literature, the average age reported in other studies was 9 and 10 years, respectively. [13] In our research, type 3b was the most prevalent genotype, but studies show that genotype 3 is more common in Asia and genotype 1 is more common in Europe and America.[14]

In our study, blood transfusion was identified as the leading cause of hepatitis C transmission, with perinatal transmission having the lowest frequency. In a study conducted in Lahore, Pakistan, 51% of childhood hepatitis B and Hepatitis C infection was associated with history of past blood

transfusion. Underlying pre-existing medical conditions were acute lymphoblastic leukaemia (15%) and thalassemia (9%).[15] These results closely concord with the results of current study and are indicative of use of less effective blood screening methods being used in our country. Contrarily, most of the industrialized countries that employ highly effective screening methods have largely eradicated blood borne transmission of viral hepatitis. As a result, perinatal transmission is the predominant mode of transmission industrialized nations .[14]

Based on our study, 96% of cases had a negative PCR test at 4 weeks, and 100% of cases had a negative PCR test at 12 weeks and SVR was maintained at 100% of EVR. On the other hand, sustained viral response (SVR) was achieved in 99% of cases at 4 weeks and 100% of cases at 12 weeks in a similar studies using Ledipasvir-Sofosbuvir without Ribavirin and with it [12-13]. In contrast to our findings, the use of interferon resulted in SVR of 79% in type 1 and 88% in genotypes 2 and 3. This demonstrates a significant difference in the outcomes of two different regimes.[16] The results of this study strongly favour use of interferon free regimens because of their high virologic response rate as well as markedly superior side effect profile.

In our study,76% of patients reported poor appetite, followed by fatigue and weakness in 64%, vomiting in 16%, and headaches and abdominal discomfort in 56% and 66%, respectively; all these resolved in a short duration. A similar study in children reported vomiting as the predominant side effect in 46% of cases below 6 years and 32% in children above 6 years, followed by diarrhoea and headache in 39% and 29% cases respectively. Other studies reported fatigue, headache, abdominal pain and nausea as main side effects of the combination therapy.[17-20]

The results of our study show that hepatitis C can be effectively treated in children between 5 to 18 years of age with a 12 week regimen of Sofosbuvir plus Ribavirin with minimal side effects. The limitation of our study was limited data based on single centre. There is a scarcity of data in the paediatric literature, indicating the need for larger multicentre studies in Pakistan and other countries. More studies should be done with 12 week therapy; these will help improve the quality of care for children infected with hepatitis C while also reducing the financial burden on families.

Another limitation of our study was duration of treatment of 12 weeks instead of the usual 24 weeks; this was due to time constraint and in engaging patients for a longer duration. However this same limitation seems to have emerged as the strong point in that a shorter duration of therapy may be as effective as the longer one. More studies need to be done to strengthen these findings.

CONCLUSION:

Twelve weeks Sofosbuvir and Ribavirin treatment of hepatitis C-infected children was highly effective, resulting in 100% sustained virologic response; and for genotype 3 (which was 80% of our patients), this shorter regimen was as good as 24 weeks regimen.

Authors Contribution:
Nagina Shahzadi: Acquisition of data, Case Management, Original Draft Preparation, Revising it critically for important intellectual content, Supervising, Final approval of the version to be submitted
Naureen Kanwal Satti: Conception and design, writing original draft, visualization, revision, final approval of the version to be submitted
Huma Arshad: Revising it critically for important intellectual content, final approval of the version to be submitted
Nadeem Hashmat: Review and editing, revising it critically for important intellectual content, conception and design, final approval of the version to be submitted

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