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Research Article

**AN OPEN LABEL, UN-CONTROLLED TRIAL OF
SOFOSBUVIR AND RIBAVIRIN COMBINATION THERAPY IN
PLACE OF INTERFERON THERAPY IN CHILDREN WITH
UNTREATED HEPATITIS C INFECTION**¹Dr .Maryam, ²Dr. Usama Sardar, ³Aman Ali¹MBBS King Edward Medical University Lahore, Pakistan.²MD Latin American School of Medicine Havana. Cuba.³Holy Family Hospital Rawalpindi**Abstract:**

Objective: To determine the safety and effectiveness of sofosbuvir and ribavirin combination therapy in children with untreated HCV infection.

Method: this is an experimental study or open labelled un-controlled trial conducted at hepatology department of Children hospital, Lahore and the Institute of Child Health, Lahore from January to December 2016. PCR positive, untreated hepatitis C infected children of age group 5 to 18 years were included in study by following consecutive non probability sampling technique. Signs, symptoms were noted and investigations (blood CP, PT, billirubin, serum ALT and PCR) were performed. Sofosbuvir 400mg 24 hourly and ribavirin 10-15mg/kg/24 hours were given to all patients, treatment duration was twenty four weeks. Patients were followed up with 4 weeks interval after treatment initiation. PCR was performed at 4 weeks duration and was repeated at 12 weeks, if positive. PCR was repeated at completion of treatment and 12 weeks after that. To analyse data SPSS version 20 was used.

Results: 35 patients were included in study with age group 10.24±2.80 years amongst which 22(62.86%) were males and 13(37.14%) were females. The commonest HCV genotype was 3, observed in 27(77.15%) patients and genotype 1 was second most common, observed in 6(17.14%) patients, while 2(5.71%) patients were untypeable. Rapid virological response and early virological response was achieved by thirty (85.71%) and five (14.28%) patients, respectively. All patients well tolerated treatment and were PCR negative at the treatment completion. Eight (22.86%) patients suffered headache, but showed rapid recovery.

Keywords: Hepatitis C virus, Untreated, children, sofosbuvir, ribavirin.

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INTRODUCTION:

Hepatitis C virus primarily infects liver and is one of the commonest diseases worldwide. It leads to chronic liver inflammation resulting in cirrhosis or hepatocellular carcinoma. Pegylated interferon α -2a and α -2b with ribavirin is effectively used against HCV in children above 3 years of age [1,2]. This regimen showed positive effects in almost 60% of patients in almost all genotypes. Side effects associated with interferon therapy include thrombocytopenia, flue like symptoms, headache, fever, myalgias and depression [3,4]. Ribavirin and interferon combination treatment is associated with anemia, hypothyroidism, but both these symptoms can be reversed by dose reduction [4]. The response to interferon based regimens differs according to various patient characters including baseline viral load, previous treatment response, cirrhosis and genotype [5]. Weekly injections, less effectiveness against genotype 1 and 4 and side effects mentioned above are various drawbacks of interferon and ribavirin therapy.

American association for the study of liver diseases and infectious disease society of America approves use of sofosbuvir in place of interferon for curing hepatitis C and its effectiveness against several genotypes. Sofosbuvir binds NS5B RNA dependent RNA polymerase and has an effective response against genotype 1,2,3,4 and 6 [8]. In December 2013, its use was approved by FDA and in Pakistan it was licensed by Drug Regulatory Authority of Pakistan in November 2014. It is effective in 93.85% patients with headache as a common side effect [9].

This research aims to determine the effective use of sofosbuvir and ribavirin combination therapy in children from 5 to 18 years of age, as less research data is available regarding effectiveness of this regimen in children.

METHODOLGY:

An un-controlled, open label trial was conducted at Children Hospital Lahore, hepatology department and The Institute of Child Health, Lahore over a period of one year after hospital ethical committee approval. Data was collected after taking informed written consent from parents or guardians. Patients admitted in wards, presenting to outdoor or referred from other health facilities between age group of 5 to 18 years suffering from hepatitis C infection, confirmed by PCR, not previously taking any hepatitis C treatment and those who had completed chemotherapy in case of carcinoma were included in study. Patients suffering from end stage renal disease (ESRD), decompensated liver disease, carcinoma,

taking chemotherapy or who underwent liver transplant or previously treated were excluded. Sample size of 35 was calculated by using WHO calculator.

A questionnaire was designed and data was collected by medical professionals; age, gender of patients was asked. On examination CLD stigmata were noted which were digital clubbing, ascites, spider angiomas, hepatosplenomegaly and palmar erythema. Investigations including blood complete picture, prothrombin time, ALT, billirubin and PCR were performed. All patients included in study were started with sofosbuvir 400mg 24 hourly and ribavirin 10-15mg/kg/24 hourly. Patients were regularly followed up after every 4 weeks in hospital outdoor. At each follow up visit patients were inquired about any treatment side effects and investigations including blood CP, PT,ALT and billirubin were performed to evaluate treatment response. PCR was performed after 4 weeks and was repeated at 12 weeks in cases who were positive at 4 weeks. This regimen was continued for 24 weeks in all patients. PCR was performed at completion of treatment and twelve weeks after that.

Effectiveness of therapy against genotypes was confirmed in terms of HCV RNA clearance by using real time qualitative PCR. Negative PCR at 4 weeks was considered rapid virological response. Positive PCR at 4 weeks but later negative at 12 weeks of therapy was considered Early virological response. Sustained virological Response was PCR negative at 12 weeks after completion of 24 weeks treatment regimen. Treatment safety was defined as safety from appearance of any side effect related to drugs which could lead to discontinuation of treatment.

Data was analysed by using SPSS version 20. Descriptive statistics were calculated. Qualitative variables i.e. sex, genotype of hepatitis C virus, stigmata of chronic liver disease, side effects and virological responses were presented in the form of percentages and frequencies. Quantitative variables including age, Hb, platelet count, TLC, prothrombin time, ALT and billirubin underwent normality testing using Shapiro-Wilk test. Mean \pm standard deviation was used to present variables with normal distribution, whereas non parametric variables were shown as median or interquartile range. Serum ALT levels before and after treatment was compared by using Wilcoxon Signed Rank Test. Hemolglobin levels before and after treatment were compared by using paired sample t-test. P value of <0.05 was considered significant.

RESULTS:

Thirty five patients were included in study with mean age group 10.24 ± 2.80 years amongst which male to female ratio was 22 and 13 respectively, which makes 62.86% and 37.14% out of total patients. Mean APRI score was noted as 0.58 ± 0.33 (range 0.10-1.32). Genotype 3 was found in 27 patients (77.15%), while genotype 1 was observed in 6 patients (17.14%), remaining 2 patients (5.71%) fell in untypeable category. Previous history of hematological disorders were present in many patients, thalassemia major was noted in 5 out of 35 patients which turned out to be 14.28% of total. Other hematologic disorders were non-hodgkins lymphoma and acute lymphoblastic leukemia present in 2 patients i.e. 5.71% each. 1 patient i.e. 2.85% was previously diagnosed for von- willibrand and hodgkins disease. Wilson's disease and rhabdomyosarcoma was found in 1 patient which was 2.85% of total sample.

Most common mode of transmission of hepatitis C was also inquired, results were blood transfusion in 15 patients, which was 42.86% of total sample. Second most common cause was perinatal transmission which was noted in 7 patients and was 20.00% of total. Past surgical history was present in 4 patients, tattooing was present in 1 patient, it was 11.23% and 2.85% respectively. 8 out of 35 (22.86%) had no risk factor.

30 out of 35 patients (85.71%) were able to achieve rapid virological response, confirmed by PCR at 4 weeks of treatment, remaining 5 (14.29%) patients

achieved early virological response and were detected PCR negative at 12 weeks of treatment. At completion of treatment all patients were detected PCR negative. Sustained virological response was achieved by 34 patients (97.14%) at twelve weeks after treatment completion.

Haemoglobin level was measured in patients before and after treatment and results obtained were, 11.49 ± 1.3 g/dl and 11.11 ± 1.66 g/dl, respectively. Change in haemoglobin level was statistically not significant as p value was 0.43. Liver function tests were also performed and serum hepatic enzymes level was reverted back to normal. Before treatment ALT level was found above normal range in 25 patients (71.43%), it was repeated at the end of treatment and all patients except 2 (5.71%) were found to have normal ALT level. P value was <0.001 , which was statistically highly significant. Median ALT before treatment was 55 IU/ml with 55 as interquartile range. Median ALT at the end of treatment was found to be 19 IU/ml with 11 as interquartile range. Almost all patients well tolerated the regimen, no patient suffered serious side effects. Only 8 patients (22.86%) suffered headache which gradually improved within 12-16 weeks of treatment. One patient had developmental delay and suffered severe headache which lead to termination of treatment after 8 weeks. However PCR of this particular patient was negative at 4 weeks and was repeated at 24 weeks, which was also negative. One patient (2.85%) suffered constipation during treatment and was started laxatives in mild dose as adjuvant to avoid this side effect.

Table:1 Virological response according to HCV genotype. (n=35)

	Frequency of genotype 1(%)	Frequency of genotype 3(%)	Frequency of untypeable genotype(%)
Total patients	6 out of 35(17.14%)	27 out of 35(77.15%)	2 out of 35(5.71%)
Virological response	6 out of 6(100%)	27 out of 27(100%)	2 out of 2(100%)
RVR(Rapid virological response)	5 out of 6(83.33%)	23 out of 27(85.19%)	2 out of 2(100%)
EVR(early virological response)	1 out of 6(16.67%)	4 out of 27(14.81%)	0 out of 2(0.0%)
SVR(sustained virological response)	6 out of 6(100%)	26 out of 27(96.29%)	2 out of 2(100%)

DISCUSSION:

In this research study 35 Hepatitis C infected children were selected, the male to female predominance was 2:1, with use of injections or transfusions as most common mode of transmission while perinatal, past surgical history and tattooing were the other modes of transmission [9]. These results closely resemble the literature and the data collected in a research conducted by Elise Roy, et.al. However in developed world use of the effective pre-transfusion screening techniques have remarkably reduced blood transfusion as mode of hepatitis C transmission, in developed world the most common mode of transmission is perinatal, as narrated by Guss D, et al [10]. In Pakistan and other developing countries where pre-transfusion screening process is not efficient, blood transfusion and use of injectable drugs is still most common cause, current research study depicted similar results regarding risk factors of hepatitis C transmission.

Interferon based therapy was being used for treatment of hepatitis C, but now due to repeated injections and side effects of interferon therapy it is being replaced by many non- injectable antiviral drugs which include sofosbuvir, dasabuvir, ombitasvir, daclatasvir, ledipasvir and paritapavir. All these drugs are under trials for their use in several combinations. Due to fewer side effects and high efficacy as compared to interferon therapy these drugs are quickly replacing interferon regimen [10]. However less data is available regarding their effectiveness and safety in paediatric age group. This research aims to find effectiveness and safety of non injectable antiviral drugs, sofosbuvir and ribavirin in children. In a study conducted by Kris V. Kowdley, et al. [11] the effectiveness of non-injectable antivirals in previously untreated or treatment failure hepatitis C infected patients was found to be almost 96%.

The research data regarding effectiveness of these drugs in children is much less as compared to that in adult age group. In a study conducted by Babusis D, et al. [12] regarding effectiveness of understudy regimen in adult population was found to be 94%. Several trials are being done worldwide in different combinations to study the effectiveness of these newly introduced drugs in paediatric age group. Most common combinations which are under trial are of sofosbuvir and ribavirin, sofosbuvir and ledipasvir [13,14].

The current research study depicts effectiveness and safe use of sofosbuvir and ribavirin in place of conventional interferon based regimen for treatment

of hepatitis C in paediatric age group. However, lot more research work is yet needed to be done to find out the efficacy and reduction in recurrence rate of HCV in children by use of these drugs. New regimen has very well depicted its role in treatment of genotype 1, which was previously considered as difficult to treat genotype amongst all others.

CONCLUSION:

Sofosbuvir and Ribavirin combination therapy is highly effective in paediatric patients suffering from hepatitis C. There are very mild side effects associated with the above-mentioned drug regimen.

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