ORIGINAL ARTICLE

TREATMENT OUTCOME OF HCV INFECTED PAEDIATRIC PATIENTS AND YOUNG ADULTS AT KARACHI, PAKISTAN

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Background: Scanty data are available regarding outcome of children and young adults treated conventionally for Hepatitis C. The present study was undertaken to evaluate the outcome of paediatric and young adult patients treated with PEG-IFN-α or conventional interferon (IFN) plus Ribavirin at a public sector hospital of Karachi. **Methods**: This was an observational study, conducted at Sarwar Zuberi Liver Centre, Civil Hospital Karachi, from 2007 to 2010. Patients up to 20 year of age were tested for Anti-HCV antibodies by 4th generation ELISA and in positive cases HCV RNA was done by PCR. Patients with HBV, HIV and other comorbids such as thalassaemia minor, haemophilia, kidney disease, and co-existing active illness other than HCV were excluded. Depending upon the genotype, patients were treated for 24–48 weeks with IFN 3 MIU ×3 per week or PEG-IFN-α (1.5 µg/Kg) per week plus Ribavirin 15 mg/Kg/day. Nearly all patients were followed till the end of treatment. **Results**: Mean age of 55 patients, was 18.42±2.59 years (range 9–20 years) and BMI 19.56±2.36 Kg/m^2. Females were 70.9% (n=39). More than 80% had genotype 3 (subtype a or b). Remaining had genotype 1, 4 or mixed. Slight decreases in haemoglobin, platelet and white cell count at 1, 3 and 6 months of treatment were noted. No significant side effects were noted. There was a marked decrease in the ALT post treatment (pre-treatment values 72.69±50.73 versus post-treatment 24.81±14.09 IU/l). End-treatment response (ETR) was 90.9%; of these sustained viral response (SVR) was achieved in 86.3%. **Conclusion**: HCV infected paediatric and young adult patients treated with PEG-IFN-α/or conventional interferon plus Ribavirin (combination therapy) achieved an ETR of 90.9% and SVR of 86.3%.

Keywords: HCV, Interferon, Ribavirin, SVR, ETR

INTRODUCTION

Hepatitis C Virus (HCV) infection causing chronic liver disease has been diagnosed and treated in adults now for a long period of time. Children infected with HCV infection have shown to have minimal progression in disease over 5–20 years. Though several studies on diagnosis, management and its effects have been published in both the paediatric and adult population little data from this part of the world is available.[1,2] The standard of care treatment is either conventional Interferon (IFN) Alpha (α) 2a (FDA approved) or 2b (Non FDA approved) 3 MIU, thrice weekly[3] or pegylated interferon (PEG-IFN) 1.5–2 µg/kg of body weight plus Ribavirin 15 mg/kg/day for 24–48 weeks depending on the genotype.[1] While the diagnosis in older children does not differ from adults[2,4] the treatment in children overall requires caution and drugs such as PEG-IFN-α/or conventional interferon are weight based. In children less than 18 months to 3 years the diagnosis of HCV infection is dependent on the status of the mother.[4] Children younger than three years of age do not receive treatment due to higher number of severe side effects and possibility of spontaneous viral clearance.

As little data are presented from this part of the world, especially from public sector hospitals, which are attended by a major population of this country, the experience of paediatric and young adults requiring treatment for HCV infection with combination therapy of PEG-IFN-α/or conventional interferon (IFN) plus Ribavirin and the outcome is described at a public sector hospital of Karachi.

MATERIAL AND METHODS

We prospectively evaluated the data of all children and young adults 9–20 years of age presenting at the liver centre of our hospital for HBV and HCV screening test. Those who were HCV positive by 4th generation ELISA were included in this study. If positive on two consecutive occasions (6 months apart) for HCV RNA PCR and with a persistently raised quantitative PCR (i.e., No. 2 log reduction from the baseline), then these patients further had HCV genotyping done.

For HCV Qualitative PCR investigation, Roche Amplicor Hepatitis C Virus (HCV) test, version 2.0 were used, which includes RNA isolation, target Amplification and Internal control detection modules.

Any patient with co-existing HBV and/or HDV, HIV co-infection, or any additional serious disease requiring admission or adjustment in the dose of interferon or Ribavirin such as renal diseases or low platelet count prior to treatment, were excluded from this study. An informed consent form approved by the Institutional Review Board was signed by every patient presenting at the liver centre. In patients less than 18 years of age consent was taken from parents.

Patients were treated for 24 weeks for genotype 3, and 48 weeks for other genotypes, with IFN 3 MIU ×3 per week or PEG-IFN-α 1.5 µg/Kg per week plus Ribavirin 15 mg/Kg/day. All patients with genotype 3

(n=51) were treated with conventional IFN and remaining (n=4) with genotype 1 and 4 with Pegylated IFN.

In all patients in whom treatment was started, baseline investigations were done including complete blood count (CBC), Alanine aminotransferase (ALT) levels, Ultrasound abdomen, and Thyroid profile. During treatment, liver function tests (LFT's) were performed monthly to monitor the degree of liver damage and response to therapy.

End treatment response (ETR) (undetectable HCV RNA by a sensitive test at the end of treatment, i.e., 24 weeks), and sustained viral response (SVR) (negative HCV RNA PCR 24 weeks after cessation of therapy) were used to define the outcome.[1]

Prior to starting and during treatment the parents of the children and young adults were counselled regarding adequate nutritional and water intake. All children and young adults were encouraged to continue normal daily activities, such as school, college, and job.

SPSS-10 was used for statistical analysis. Variables were defined qualitatively and quantitatively and Mean±SD calculated.

RESULTS

Mean age of 55 patients was 18.42±2.59 year (range 9–20 year), and BMI was 19.56±2.36 Kg/m^2. Thirty-nine (70.9%) were female. (Table-1). Eighty-nine percent of patients had genotype 3 (a or b subtype). Of these, genotype 3a was present in 83.6% and 9% were 3b. Remaining had genotype 1, 4, or mixed. A slight decrease in haemoglobin, platelet and white cell count (WBC) was noted at 3, and 6 months of treatment when compared with pre-treatment values (Table-2). There was a marked decrease in the ALT pre-treatment vs post-treatment. End treatment response (ETR) was 92.7%, of these sustained viral response (SVR) was achieved in 89.09% (Table-3).

Fever was the commonest side-effect seen in 60% (n=33) in first month gradually decreasing to 25.5% (n=14) in 6th month of therapy. Occasional fever, was satisfactorily controlled with antipyretics. Other side-effects such as anorexia, depression, thrombocytopenia, vomiting, headache, fatigue, inflammation at the site of injection were not prominent in our cohort of population. All school-going children continued to attend school. Nearly all patients maintained their pre-treatment weight with slight or no loss of weight. The overall compliance of the patients was good. The parents were counselled for proper follow-up, and all patients were followed till the end of the study. No significant side-effects were noted. Majority of our patients (19/20, 95% <18 years, and 21/24, 87.5% >18 years) had an ETR; while, 18/20 (90%) <18 years and 20/24 (83%) >18 years had achieved an SVR. Remaining SVR results are awaited.

Table-1: Demographic data of Hepatitis C infected patients

Variables	<18 Year (n=25)	>18 Year (n=30)
Mean age (Year)	14.13±2.75	19.50±0.86
Male	10	6
Female	15	24
Mean BMI (Kg/m^2)	19.31±3.47	19.74±1.46
HCV Genotypes		
3a	22	24
3b	0	5
Others*	3**	1†

*genotype 1, 4 and mixed, **2 patients were of genotype 1 and 1 was mixed 3a and 3b, †genotype 4 patient

Table-2: Laboratory data of Hepatitis C infected patients (n=55)

Laboratory Test	0 month	3rd month	6th month
Haemoglobin (Hb) g/dl	12.02±2.14	11.23±1.42	10.74±1.60
Platelet (10^3/µl)	216.17±68.61	197.33±74.82	172.90±38.32
WBC (10^3/µl)	6.4±1.75	5.7±2.0	5.18±1.42
ALT (U/L)	72.69±50.73	31.29±12.53	24.81±14.09

Table-3: Treatment outcome of HCV infected patients

Age Group	ETR	SVR
<18 Year (n=25)	24	23
>18 Year (n=30)	27	26

DISCUSSION

Hepatitis C is a known problem in South East Asia, with a prevalence of 2.1%.[5] Approximately 0.2% of 6–12 year olds and 0.4% of 13–19 year olds (174,000 children) are Anti-HCV positive in the United States.[66] However, there are little data on HCV infection and its treatment in children from our part of the world. RCT trials have also been done for treatment of HCV infection in children outside Pakistan.[2,7–9] In these studies genotype differed substantially from study to study. The study done by Schwarz *et al* included predominantly children with HCV genotype 1 infection.[9]

Children were initially given conventional or pegylated interferon plus ribazole as per recommended doses.[1] The optimal doses of PEG-IFN-α-2b and α-2a are 1.5 µg/Kg/week and 180 µg/week subcutaneously, respectively, whereas that of Ribavirin is 800–1,200 mg (genotype 2 and 3) and 1,000–1,400 mg/day (genotypes 1 and 4), depending upon body weight.[1,2,4,9,10] Majority of the children managed with conventional or PEG interferon responded well to treatment in concordance with other published studies outside Pakistan. Our data showed ETR and SVR to be similar to that in the adult population in terms of genotype 3, however, the response in the younger children, i.e., less than 18 years was better both in terms of outcome of treatment and tolerability of drug than the adult population supportive of other studies.[11–13]

Unlike adults[1], side-effects noticed in children were minimal. Though reason for this is not clear, but other studies done on children also shows that they appear to tolerate interferon therapy much better and with fewer or no serious side effects.[11,12] Majority of our patients continued their normal daily routine including

school activities without any difficulty despite receiving therapy. As mothers were counselled repeatedly about their children, taking small, frequent and proper meals hence, there was minimal or no weight loss observed during treatment.

The ETR and SVR rates achieved in this cohort of patients were 92.7% and 89.09% respectively. Jara *et al* have showed an SVR of 50% (3/3 in genotype 3 and 12/27 in genotype 1/4).[14] These higher rates of SVR in children might be the result of earlier stage of disease, higher relative IFN dosage and lack of comorbid conditions.[15] A recent comparative analysis of efficacies of different therapeutic options available for children has revealed that pegylated interferon plus Ribavarin combination therapy yields better results, in terms of ETR and SVR, as compared to conventional interferon therapy.[15] Studies show that genotype 3 is the commonest genotype in Pakistan.[16] This is also our observation and majority of our patients (n=51) had genotype 3, of which genotype 3a were 83.63% (n=46). These patients are easier to treat with less duration of treatment, higher SVR rates and less progression to fibrosis.

Adverse effects with IFN and Pegylated IFN plus Ribavarin are common and particularly can involve events related to leucopenia and neutropenia, these may be severe enough to require a dose reduction.[4] Our patients showed a decrease in haematological markers over a period of 6 months but none required dose reduction.

Though little is known about correlation between EVR and SVR in children, a recent pilot study showed that SVR occurred in 72% children with a 2-log reduction from baseline after 12 weeks but in none whose viral levels did not decrease by this time.[17] Many international studies especially large clinical trials show similar results. In a large review of paediatric IFN trials SVR occurred in 27% and 71% those infected with HCV genotypes 1 and HCV genotypes 2–3, respectively.[18,19] Safety and efficacy of the combination therapy has also been documented.[16] A more recent trial also shows genotype to be the main predictor of response with genotype 2 and 3 showing an SVR of 93%.[20] Last two studies are in agreement with our study where majority 86.3% of our patients with genotype 3 had achieved an SVR, with minimum side effects.

CONCLUSION

Children with HCV achieved a sustained virological response and tolerated the therapy without a disturbance in their school activities and growth parameters. A limitation of our study was our inability to do a rapid virological response (RVR) or early virological response (EVR) due to cost issues in our cohort of patients.

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