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Research Article

Treatment of Chronic Hepatitis C in Egyptian Children with Pegylated Interferon α 2b Plus Ribavirin

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Abstract

Introduction: Hepatitis C virus (HCV) Viral hepatitis is a very common health problem in Egypt. Liver fibrosis in pediatric patients tends to increase with age showing slow progressive histologic injury. The aim of our study is to determine the efficacy and safety of pegylated interferon (peg-IFN) alfa-2a plus ribavirin (RBV) in children with chronic hepatitis C virus (HCV).

Methods: Fifty children with chronic HCV infection. The diagnosis of CHC was made by a persistent or intermittent elevation of alanine aminotransferase (ALT, the upper limit of normal ALT is 40 IU/L) over a six-month period, anti-HCV positivity and detection of HCV-RNA in the sera. Fifty patients received antiviral therapy consisting of Peg- IFN-α 2b with a dose of 60 ug/1.73m^2/week subcutaneously. According to sustained virological response (SVR) (undetectable HCV RNA at 24 weeks after treatment completion), patients were classified into two groups, responders and non- responders.

Results: Responders: Patients who achieved SVR, they were 34 patients, 19 males and 15 females with age range 10.1 ± 3.2 years.

Conclusion: Therapy with pegylated interferon α2a and ribavirin is well tolerated in the pediatric age group; Pre-treatment lower viral load and lower grade of fibrosis are good parameters for detection of response.

Keywords: *Interferon; Liver Biopsy; Pegylated Interferon; Ribavirin*

Introduction

Hepatitis C virus (HCV) Viral hepatitis is a very common health problem in Egypt. The causes of mortality chronic hepatitis C virus (HCV) are liver fibrosis, cirrhosis and cancer. The recently used oral direct-acting antivirals (DAAs) provide opportunities for reducing the progress HCV disease [1].

Hepatitis C virus infection, RNA virus has the tendency for chronic infection. It affects over 180 million individuals worldwide it with significant economic impact [2].

Routine screening of the blood products has eliminated transmission via transfusion, the most common mode of infection in children is vertical transmission [3]. Factors increased the risk of vertical HCV transmission are prolonged rupture of membranes, exposure to contaminated maternal blood, fetal anoxia at the time of delivery and placement of fetal scalp monitors [4].

Parenteral infected children showed higher spontaneous viral clearance, however in vertically infected children, viral clearance depended on HCV genotype and was found to range from 2.4% to 25%. Children infected with genotype 3 had a higher spontaneous clearance rate than those infected with genotype. In general spontaneous viral clearance became unlikely beyond age 4 years [5].

Liver fibrosis in pediatric patients tends to increase with age showing slow progressive histologic injury. Progression to cirrhosis in childhood although uncommon, has been reported [6].

The US Food and Drug Administration (FDA), European Medicine Agency, and the Polish group have approved the use of PEG-IFN-2a and 2b for the treatment of HCV [7].

Sofosbuvir (Sovaldi) and the combination product, ledipasvir/sofosbuvir (Harvoni), are approved for chronic HCV infection in pediatric patients aged ≥12 years or who weigh at least 35 kg [8].

Aim of the Study

The aim of our study is to determine the efficacy and safety of pegylated interferon (peg-IFN) alfa-2a plus ribavirin (RBV) in children with chronic hepatitis C virus (HCV).

Patient and Method

Fifty children with chronic HCV infection who were registered and followed-up from June 2010 till April 2016 were included in the primary selection. Pa¬tients with the following conditions were excluded; (1) co-infection with hepatitis B virus (HBV), (2) peripheral blood neutrophil count < 1.5×10^3/ml or platelet count < 70×10^3/ml or hemoglobin level lower than 10 g/dl, (3) concomitant serious medical illnesses, such as; malignancy, autoimmune diseases, severe cardiopulmonary disease, uncontrolled diabetes mel¬litus, or thyroid diseases.

Blood samples from all patients for liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl-transferase (GGT), total bilirubin (TB) direct bilirubin (DB), total proteins (TP) and Albumin (Alb); these tests were carried out using Integra 400 auto analyzer Roche diagnostics Corporation 9115, Hague Road, Indiana Polis USA.

Viral markers were done using ELISA technique. HCV antibodies for both groups were done by kit from inngenetics, Ghent- Belgium [9]. Hepatitis B virus surface antigen (HBsAg) for both groups and HBV core antibodies [(HBcIgM) and (HBcIgG)] were done by ELISA technique, by kit from Sorin Biomedica Co, Spain [10].

The diagnosis of CHC was made by a persistent or intermittent elevation of alanine aminotransferase (ALT, the upper limit of normal ALT is 40 IU/L) over a six-month period, anti-HCV positivity and detection of HCV-RNA in the sera (for positive HCV antibodies only), It was done using COBAS Ampliprep/COBAS TaqMan, Roche Molecular Systems, Inc., Branchburg, NJ, USA [11]. It is a nucleic acid amplification test for the quantification of HCV-RNA.

Liver biopsy was done for the diseased group only, after sedation using midazolam (0.3 mg/kg/dose), by true cut needle before IFN therapy. Biopsy specimens were fixed in formalin-buffered saline, embedded in paraffin followed by a histological examination using hematoxylin and eosin stains, orcien stain and Periodic acid Schiff (PAS) stain for routine histopathological evaluation. Hepatic necro-inflammatory activity and liver fibrosis were evaluated according to Ishak staging and grading scores [12].

Fifty patients received antiviral therapy consisting of Peg- IFN-α 2b with a dose of 60 ug/1.73m2/week subcutaneously (peg-intron, Schering-Plough Brinny, U.S.A) plus ribavirin 15 mg/kg/day orally.

According to sustained virological response (SVR) (undetectable HCV RNA at 24 weeks after treatment completion), patients were classified into two groups, responders and non- responders.

The study was revised and approved by the local ethical committee and institutional review board (IRB) of National Liver Institute.

Statistical analysis

Data were analyzed using the SPSS package for Windows, version 18.0, SPSS Inc., Chicago, Illinois, USA. Qualitative data were expressed as frequency and percentage. Quantitative data were shown as mean ± Standard deviation (SD).

Results

Fifty children divided diagnosed as chronic HCV 28 males and 22 females, mean age was 11.1 ± 2.4 years, treated with Peg- IFN-α 2b with a dose of 60 ug/1.73m^2/week subcutaneously plus ribavirin 15 mg/kg/day orally, divided into 2 groups, responders (34 patients 68%) and non-responders (16 patients 32%).

Responders: Patients who achieved SVR, they were 34 patients, 19 males and 15 females with age range 10.1 ± 3.2 years.

Non responders: Patients who didn't achieve SVR. They were 16 patients, 9 males and 7 females with age range 12.4 ± 3.8 years.

Family history of HCV infection in 24 patients, History of surgical operation in 31 patients, Skin piercing 31patients, dental procedures in 11 patients while history of blood transfusion in 3 patients only. No of our children had been previously treated with interferon and ribavirin.

Necro-inflammatory activity in liver biopsies was minimal in 28 patients, mild in 17 patients and moderate in 3 patient while no activity in 2 two.

Fibrosis in liver biopsies of the studied patients mild in 37 patients, moderate in 9, no one of our patients had severe fibrosis. Four patients had no fibrosis.

Pretreatment serum level of HCV-RNA was 765217.18 ± 1574231.42 in responders group, while was 1698342.5 ± 3987876.11 (p value was 0.24).

Early virological response (EVR) was observed in 40 patient 80%, while sustained virological response (SVR) was 68%.

Stage of fibrosis was mild in 31.25% in non-responders while it was 79.4% among responders, moderate fibrosis seen in 56.25% of non-responder group, while 5.9% of the same group had moderate fibrosis.

The most commonly observed side effects was fever, myalgia and bony ache, Flu-like symptoms observed in almost all cases specially with first injections, then fade gradually. All cases were managed with oral Paracetamol. Poor appetite also was a frequent family complains.

Leucopenia, anemia and thrombocytopenia commonly observed but not reaching the level indicated to discontinue the treatment in the studied group. None of our patients had thyroid dysfunction.

Possible risk factors	Chronic HCV children (n = 50)	
	N	%
History of blood transfusion	3	(6)
History of surgical operation	31	(62)
Family history of HCV infection	24	(48)
History of dental procedures	11	(22)
Skin piercing	21	(42)

Table 1: *Possible risk factors of HCV infection.*

Parameters	Chronic HCV children (n = 50) Mean ± SD
TB (mg/dl)	0.57 ± 0.23
DB (mg/dl)	0.14 ± 0.09
TP. (g/dl)	6.7 ± 0.49
Alb. (g/dl)	3.9 ± 0.71
AST (U/L)	38.46 ± 17.35
ALT (U/L)	42.60 ± 15.70
GGT (U/L)	222.65 ± 139.11
ALK (U/L)	274.84 ± 164.45
P.T (sec)	11.03 ± 0.87

Table 2: *Liver functions tests of the studied patients.*

Factors	Chronic HCV children (n = 50)	
	n	%
No activity	2	(4)
Minimal	28	(56)
Mild	17	(34)
Moderate	3	(6)

Table 3: *Necroinflammatory activity in liver biopsies of the studied patients.*

Stage of fibrosis	Chronic HCV children (n = 50)	
	n	%
No fibrosis	4	(8)
Mild	37	(74)
Moderate	9	(18)
Severe	0	(0.0)

Table 4: *Fibrosis in liver biopsies of the studied patients.*

Sex	Responders n = 34		Non-responders n = 16		P-value
	N	%	n	%	
Male	19	(55.88)	9	(56.25)	0.198
Female	15	(44.12)	7	(43.75)	

Table 5: *Comparison between responders and non-responders regarding sex.*

Parameters	Responders n = 34 mean ± SD	Non-responders n = 16 mean ± SD	P-value
Pretreatment serum HCV- RNA (IU/ml)	765217.18 ± 1574231.42	1698342.5 ± 3987876.11	0.24

Table 6: *Comparison between responders and non-responders regarding pretreatment serum level of HCV-RNA.*

Stage of fibrosis	Non-responders n = 16		Responders n = 34		P-value
	n	%	n	%	
No fibrosis	2	(12.5)	5	(14.7)	0.1
Mild	5	(31.25)	27	(79.4)	
Moderate	9	(56.25)	2	(5.9)	
Severe	0	(0.0)	0	(0.0)	

Table 7: *Comparison between responders and non-responders regarding stage of fibrosis in liver biopsy.*

Discussion

Peg-IFN plus RBV is effective in the majority of children and adolescents with chronic HCV. Side effects are common, but rarely result in discontinuation of treatment.

This study showed the response rate was 68%, which differ with many studies [13], who studied the same age group was reported 78.9% of children respond to treatment, while [14] reported SVR was achieved in 29 of 55 (53%) in children received combination therapy. This difference may be due to different genotypes.

This result is much higher than the standard non Pegylated Interferon was associated with < 33% SVR.

Pretreatment serum HCV- RNA viral load is observed to be effective parameter detecting the response to treatment in this study (P < 0.5), also approved by other studies [15]. A genetic polymorphism near the IL28B gene on chromosome 19 has been found to be highly predictive of viral clearance with PEG-IFN and ribavirin, which explains some of the association between response rate and ethnicity [16].

The fibrosis grade in the analyzed groups did not exceed moderate and the ALT level n mean 42.51 ± 12.65 IU/L n are important factors. This is can be explained by the short period of time between infection and histopathologic evaluation. Low grade of fibrosis may further explain the higher SVR noticed in children.

Serum ALT levels have no consistent relationship to liver histologic findings. The following side effects were observed during the treatment: fever, flu like symptoms, headache, redness at the injection site and poor appetite. Laboratory test abnormalities were neutropenia and reduced hemoglobin levels; thrombocytopenia. All of these finding did not need discontinuation of treatment or even reduction of the doses.

More effective medications are available nowadays specially in adults. New oral drugs have been licensed by European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for treatment of adults with chronic HCV. These drugs achieved high (>90%) SVR rates in 12 weeks, with different viral genotype, stage of fibrosis, and of co-infection with human immunodeficiency virus (HIV).

Ledipasvir/sofosbuvir and the combination of sofosbuvir and ribavirin have been approved by FDA and EMA in April and June to July 2017, respectively. These drugs can be used for treatment of adolescents (12–17 years) or children weighing more than 35 kg with chronic HCV genotype 1, 4, 5, and 6 and genotype 2 and 3 infections, respectively. Children younger than 12 years can be treated with the dual therapy of PEG IFN a-2a or -2b and ribavirin [17].

Conclusion

Therapy with pegylated interferon α2a and ribavirin is well tolerated in the pediatric age group; Pre-treatment lower viral load and lower grade of fibrosis are good parameters for detection of response.

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