REVIEW PROF-2172

HEPATITIS C IN CHILDREN;

Its management

Dr. Abdul Rehman.

ABSTRACT….. The knowledge of the hepatitis C management in children is scanty but rapidly growing. This review will discuss the update in the management of the disease in children. **Abbreviations:** Hepatitis C virus (HCV); International unit (IU); Polymerase chain reaction (PCR); Sustained virological response (SVR); Rapid virological response (RVR); Early virological response (EVR); End-of-treatment response (ETR)

Key words: Sustained virological response; Peginterferon alfa-2a; Peginterferon alfa-2b; Ribavirin; Chronic hepatitis C; Management; Adverse effects; Liver biopsy.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a major global health problem and about 70-100,000 children are infected with HCV. Although HCV can lead to liver transplantation and death during childhood but the disease acquired during childhood have slow progression[1]. Approximately 2% cases may experience rapid histological progression to liver cirrhosis during early childhood[2].

TO TREAT OR NOT TO TREAT

Treatment is avoided in acute hepatitis as there are 25–50% chances of spontaneous resolution and fulminant hepatic failure from HCV has not been described in children[3].

The pharmacological efficacy of peginterferon and ribavirin seems to be proven but there are different opinions about 'who, when and how to treat children infected'[4]. Robinson et al reviewed the literature and concluded that there is no clear indication for antiviral therapy in the majority of children with HCV infection[1]. The arguments in favour of treatment of chronic hepatitis (detectable serum HCV RNA for longer than 6 months) are that it prevents disease progression, removes social stigma, reduction of long-term morbidity, cost-effectiveness on a drug-per-weight basis, and elimination of the virus before life events or behaviors that promote transmission (pregnancy and delivery, or intravenous drug use)[5] . Overall the quality of life and psychosocial functioning are not deteriorated by the treatment of children with HCV[6]. The arguments against the treatment are that HCV is mild in most children and the morbidity is delayed, subjecting them to up to 1 year of subcutaneous injections with possible adverse drug effects is as yet unwarranted, and is costly for families[5]. For the majority of HCV-infected children showing minimal fibrosis on biopsy and no active hepatitis, there is no data to support immediate therapy[5]. Children with hepatitis C who demonstrate persistently elevated serum aminotransferases or those with progressive disease (i.e. fibrosis on liver histology) should be considered for treatment[7].

AIM OF TREATMENT AND TERMINOLOGY

The aim of therapy is to achieve negative conversion of HCV viremia to a level below the detection limit of the qualitative polymerase chain reaction (PCR) technique employed (10–50 IU/ml). Once negativity has been achieved, treatment must continue long enough to ensure eradication of the infection from the liver[8]. Several types of virological responses are used to assess efficacy, labeled according to their timing relative to treatment. These are tested sensitive PCR based quantitative assay which may detect HCV RNA

as low as 10 IU/ml. The definitions of these virological responses are based on the recommendations of American Association for the Study of Liver Diseases 2009[9].

RAPID VIROLOGICAL RESPONSE (RVR)

HCV RNA is negative in the serum at treatment week 4.

EARLY VIROLOGICAL RESPONSE (EVR)

$\geqslant$ 2 log reduction in HCV RNA level in the serum but not negative as compared to the baseline HCV RNA level (partial EVR) or HCV RNA level negative in the serum at treatment week 12 (complete EVR).

END-OF-TREATMENT RESPONSE (ETR)

HCV RNA negative in the serum at the end of treatment (which may be either 24 or 48 weeks).

SUSTAINED VIROLOGICAL RESPONSE (SVR)

HCV RNA negative in the serum 24 weeks after cessation of treatment.

BREAKTHROUGH

Reappearance of HCV RNA in the serum while still on therapy.

RELAPSE

Reappearance of HCV RNA in serum after therapy is discontinued.

NONRESPONDER

May be "null responder" or "partial responder (Failure to clear HCV RNA from serum after 24 weeks of therapy.

DRUG THERAPY

The peginterferon alfa with or without ribavirin, like in adults, has been used in the treatment of chronic hepatitis C in children. The studies[10,11,12,13,14,15] in which peginterferon α-2b was used in children are shown in table-I while studies in which peginterferon α-2a were used[16,17,18] are shown in table-II. These studies used peginterferon α-2b in a dose of 1-1.5 mg/kg/week and ribavirin in a dose of 15 mg/kg/day except in the study by Baker et al 2007[11] who used ribavirin 800 mg/day as the ages of patients were 14-17 years. The dose of peginterferon α-2a used in these studies was 100 ug/m2 once weekly while ribavirin, if used, in the same doses as with peginterferon α-2b. Schwarz et al 2006[16] used only peginterferon α-2a while Schwarz et al 2011[17] compared the two group, one with ribavirin and other without ribavirin and found that combination therapy was better than monotherapy. Recent studies in adults[19,20,21] have shown the superiority of α-2a with equal or better safety over α-2b but there are no randomized studies available in children to compare these two peginterferons in children. It is not possible to infer which peginterferon is better in children. The Infectious Diseases Society of America and the American College of Gastroenterology 2009 recommended the use of peginterferon alfa-2b with ribavirin for hepatitis C in children in a dose of 60 ug/m2 weekly given subcutaneously in combination with ribavirin 15 mg/kg daily in 2 divided doses[9] but these recommendations might be reconsidered to include peginterferon α-2a in combination with ribavirin for the treatment as well.

Different HCV genotypes exhibit different sensitivities to treatment both in children and adults. The SVR rates are higher in children with genotype 2 or 3 as compared to genotype 1 and 4[11,12,13,14,17,18]. The SVR rate in genotypes 2 and 3 are 73.3%-100% if treated for 24 weeks while genotypes 1 and 4 show overall SVR rate 22%-54.5% with 48 weeks of therapy as shown in table-I and II.

Name of the study	Kowala-Piaskowska et al 2007 (10) Total cases studied=30 Age of studied group 8-19 years	Baker et al 2007 (11) Total cases studied=10 Age of studied group 11-18 years	Jara et al 2008 (12) Total cases studied=30 Age of studied group 3-16 years	Tajiri at al 2009 (13) Total cases studied = 37 Age of studied group 7-30 years	Wirth at al 2010 (14) Total cases studied = 107 Age of studied group 3-17 years	Al Ali at al 2010 (15) Total cases studied = 12 Age of studied group 14-17 years
Early viral response (EVR) both complete and incomplete	*-	*-	70% cases (out of which 71.43% was complete EVR while 28.57% partial EVR)	*- Complete EVR in 86% cases	*- Complete EVR in 60% of cases of genotype 1 2 87% 3 87% 4 80%	*- Complete EVR in 83% cases
End treatment response (ETR)	70% cases	70% cases	60% cases (ETR in case with genotype 3 was 100%, with genotype 1 was 58% and with genotype 4 was 00%)	*-	ETR in cases with genotype 1 was 60%, with genotype 2 was 93%, with genotype 3 was 93% and with genotype 4 was 80%	10 (83%) cases at 48 weeks of treatment
Sustained viral response (SVR)	70% cases	30% cases (SVR in cases with genotype 1 was 22% while with genotype 2 was 100%)	50% cases (SVR in cases with genotype 3 was 100%, with genotype 1 was 44% and with genotype 4 was 00%)	73% cases (SVR in cases with genotype 2 was 54.5% and with genotype 2 was 73.3%)	65% cases (SVR in cases with genotype 1 was 53%, with genotype 2 was 93%, with genotype 3 was 93% and with genotype 4 was 80%	9 (75%)
Breakthrough	*-	10%	6.6%	-	*-	-
Relapse	13%	40%	3.3%	15%	1%	8%
Nonresponder	30%	10%	40%	3.3%	*-	17%
The lowest limit of HCV RNA detected by the test used	50 IU/ml	10 IU/ml	50 IU/ml	50 IU/ml	125 IU/ml	50 IU/ml
Genotype causing infection	Genotype 1 responsible in 97% while genotype 4 in 3% cases	Genotype 1 responsible in 90% while	Genotype 1 responsible in 87%, genotype 3 in 10% while genotype 4 in 3% cases	Genotype 1 responsible in 59% while genotype 2 in 41% cases	Genotype 1 responsible in 67%, genotype	Genotype 4 responsible for 100%
Mode of acquiring infection Vertical Parenteral Unknown	-	30% 60% 10%	70% 30% 0%	38% 59% 3%	70% 11% 19%	18% 42% 42%
Liver histopathology of studied children	Mild severity of disease and staging not exceeding 2 points	Grade I was in 70% cases while grade 2 in 30% cases	Knodell index of 1-8 <4 was 58%, 4-7 in 31% while ≥8 in 10% while there was no case of cirrhosis	-	Metavir score showed F0 in 12.5%, F1 in 84.6%, F2 in 1.9%, F3 in 1% while none had cirrhosis. Steatosis was absent in 71% while ≤5% in 22% cases	Histologic grade was 1.67 (mean) while fibrosis score was 0.67 (mean) according to Metavir score.
Case with normal ALT level	-	40% cases	6.66% cases	27% cases	59% cases	17% cases
Children with history of use of interferon or ribavirin therapy in the past	6 children	3 children	6 children. Only 1 of these children achieved SVR in this study	18 cases. SVR achieved, during this study, in these cases was 67%	Excluded	-
Any special comments on cases recruited	20 cases of pediatric malignancy were included Autoantibodies were tested at the start of study.	3 cases of hemophilia 3 and on case of IV drug user were included.	One case of clotting factor X deficiency, on case of agammaglobulinemia, one case of acute lymphocytic leukemia and three cases of cardiomyopathies were included. Autoantibodies were tested at the start of study.	7 cases of malignancy in, 5 cases of trisomy 21 were included, in 5 cases Autoantibodies were tested at the start of study.	-	None
Ribavirin dosage in per kilogram per day	15/mg/kg	Ribavirin 800 mg/day as the age of patients are 14-17 years	15/mg/kg	15/mg/kg	15/mg/kg	15/mg/kg

Table-I. Studies in children treated a2b ± ribavirin c

**-exact value is unknown -no data is available N number*

Name of the study	Schwarz et al 2006 (16) Total cases studied 14 Age of studied group 2-8 years	Sokal et al 2010 (18) Total cases studied 65 (group A 18 while group B 47 cases)** Age of studied group 6-17 years	Schwarz et al 201108 (17) Total cases studied 114 Age of studied group 5-18 years	
			Combined therapy (peginterferon plus rebavirin) Total cases studied 55	Mono therapy (peginterferon only) Total cases studied 59
Early viral response (EVR) both complete and incomplete	50% cases (complete EVR in 86% while partial EVR in 14% cases)	83% cases in group A while 57% cases in group B	*-	*-
End treatment response (ETR)	50% cases	94% cases in group A while 57% cases in group B	65% cases	37% cases
Sustained viral response (SVR)	43% cases (all were from genotype 1)	89% cases in group A while 57% cases in group B	53% cases (47% in cases with genotype 1 while 80% in case genotypes 2-3)	201% cases (17% in case with genotype 1 while 36% in genotype 2-3)
Breakthrough	7%	*-	15%	8%
Relapse	7%	*-	17%	45%
Nonresponder	43%	*-	*-	*-
The lowest limit of HCV RNA detected by the test used	50 IU/ml	50 IU/ml	50 IU/ml	50 IU/ml
Genotype causing infection	Genotype 1 responsible in 93% while non-genotype 1 in 7% cases	Group A (genotype 3 responsible in 11% cases) Group B (genotype 1 responsible in 96% while genotype 4 in 2% cases) Type 5 2%	Genotype 1 responsible in 82% while genotype 2-3 in 18% cases	Genotype 1 responsible in 80% while genotype 2-3 in 20% cases
Mode of acquiring infection Vertical Parenteral Unknown	 79% cases 7% cases 14% cases	Group A (vertical in 55.5%, parenteral in 38.9% and unknown in 5.5% cases) Group B (vertical in 42.5%, parenteral in 29.8% while unknown in 27.7% cases)	 71% *- *-	 80% *- *-
Liver histopathology of studied children	None of the child had fibrosis according to Ishak's modified histological activity index used.	No fibrosis in 44.4% cases of group A while no fibrosis in 55.3% cases of group B according to Metavir score used.	-	-
Cases with normal ALT level	None	Normal ALT level in 55% cases of group A and in 43% cases of group B.	*-	*-
Children with history of use of interferon or ribavirin therapy in the past	Excluded	Not mentioned	Excluded	Excluded
Any special comments on case recruited	-	-	-	-
Riavirin dosage in per kilogram per day	Not used	15 mg/kg	15 mg/kg	Not used

Table-II. Studies in children treated with peginterferon a-2a ± ribavirin

**-exact value in unknown -no data is available*

***Group A having infection with genotype 2,3 while group B having infection with genotype 1,4,5,6*

Drug dose modification Drug stopped***

Baker et al 2007[11] and Jara et al 2008[12] treated genotype 2 and 3 for 24 weeks, Wirth et al 2010[14] treated genotype 2 and the genotype 3 having viral load $<$600,000 iu/ml for 24 week while for 48 weeks if viral load $\geqslant$ 600,000 iu/l but treatment was stopped at 24 weeks if HCV RNA was positive at 24 weeks or $<$ 2 log reduction in HCV RNA at 12 weeks of treat and Tajiri et al 2009[13] treated genotype 2 with 24 or 48 weeks with peginterferon α-2b. Baker et al 2007[11], Jara et al 2008[12] and Al Ali et al 2010[15] treated genotype 1 and 4 for 48 weeks, Tajiri et al 2009[13] treated genotype 1 for 48 weeks. Kowala-Piaskowska et al 2007 treated

genotype 1 and 4 for 48 weeks but treatment was stopped at 24 weeks if no virological response (except in 4 cases where 48 weeks treatment was given)[10]. Wirth et al 2010[14] treated the genotype 1 and 4 for 48 weeks but the treatment was stopped at 24 weeks if HCV RNA was positive at 24 weeks or < 2 log reduction in HCV RNA at 12 weeks of treatment with peginterferon α-2b.

Schwarz et al 2006[16] treated genotype1 for 48 weeks. Sokal et al 2010[18] treated genotype 2 and 3 for 24 week while genotype 1,4,5 and 6 for 48 weeks if HCV RNA became negative at 24 weeks[18]. Schwarz et al 2011[17] treated genotype 1, 2 and 3 for 48 weeks but treatment was stopped at 24 weeks if HCV RNA positive[17] with peginterferon α-2b

Jara et al 2008[12] showed that the proportion of patients who attained HCV RNA negativity increased with time during the first 24 weeks of therapy of all genotypes but prolongation of treatment beyond 24 weeks (i.e. 48 weeks) in cases of Genotype 1 and 4 did not improve viral clearance or SVR[12]. Tajiri et al 2009[13] showed that 16 out of 22 patients with genotype 1 received 48-week therapy and 12 of the 16 achieved a SVR. The other four had 72-week therapy and all of them achieved a SVR. The Infectious Diseases Society of America and the American College of Gastroenterology 2009 recommended duration of treatment in children for 48 weeks irrespective of genotype[9]. Hu et al 2010[22] in a systematic review showed that there was insufficient data to assess the applicability of the week 12 stop rule (stopping therapy at week 12 if there is less than a 2 log drop in HCV RNA) or the efficacy of shortening therapy to 24 weeks in children with genotype 2 and 3. If HCV RNA remains detectable between 12 to 24 weeks of therapy, therapy may be extended to 72 weeks[13].

Although there is insufficient data but it may be may be proposed that, due to the high probability of a favorable response in the case of a sensitive genotype (2,3 genotypes), all patients with genotype 2 and 3 be treated for 24 weeks while in the case of less-sensitive genotypes (1,4 genotypes), re-evaluation be carried out after 24 weeks. If at this point the viral load is negative, treatment is continued up to 48 weeks, otherwise the treatment may be withdrawn, since healing is unlikely to occur even if the full treatment course is administered[12,18].

The minimum age at which peginterferon α-2a used was 2 years[16] while for peginterferon α-2b it was 3 years[12]. The Infectious Diseases Society of America and the American College of Gastroenterology 2009 also recommended that all children with chronic hepatitis C with a minimum age of two years should be considered appropriate candidates for treatment[9].

ADVERSE EFFECTS OF PEGINTERFERON ± RIBAVIRIN

The adverse effects of peginterferon plus ribavirin are similar to those associated with conventional interferon plus ribavirin but involve fewer injections and immediate injection reactions. The adverse effects noted in different studies done in children on peginterferon ±ribavirin are shown in table-III. Febrile convulsions are a hazard in younger children but the problem did not occur. Reduction or discontinuation (temporary or permanent) of interferon and/or ribavirin may ameliorate adverse effects. However, this may also jeopardize the success of treatment[9,23].

Leucocyte, neutrophil and platelet counts tend to decrease during the initial period of treatment and, subsequently, these counts stabilize but may stay below the normal range for the remainder of the treatment period increasing rapidly to baseline values after the completion of treatment[18].

Weight loss/height inhibition may occur during the treatment phase but most patients experience compensatory weight gain after the stoppage of treatment[12,14,10]. Endocrine abnormalities may occur

during treatment. Detectable antithyroid antibodies are particularly common and clinical hypothyroidism may occur, which rarely become permanent[10,12,13,14,15]. In other instances abnormally high levels of thyroid-stimulating hormone may occur[14,18]. Rarely thyrotoxicosis may develop[12,18]. Insulin dependant diabetes mellitus may develop very rarely[15,17]. Very limited data shows that in those children who have not received interferon HCV infection associated ophthalmologic changes do not occur[24]. The ophthalmologic complications are infrequent (2-3%) in children who are treated with peginterferon α-2b for HCV but these complications may be serious e.g. ischemic retinopathy and uveitis necessitating, prospective ocular assessment[17,24]. The effects on eye may be irreversible in adults[25] but because of limited data in children no inference can be drawn.

The most common adverse effect of ribavirin is a reversible hemolytic anemia, which occurs due to accumulation of phosphorylated ribavirin in erythrocytes which shortens the life span of erythrocytes. A fall in hemoglobin level between 2 and 3 g/dL within 4 weeks of starting combination therapy is common[23]. Reticulocyte count increases during therapy but returns to normal thereafter[12]. Anemia is the most common reason for ribavirin dose reduction or treatment discontinuation. Ribavirin may also cause

Adverse Effect	Range (%)	Drug does modification*	Drug stopped**
Blood			
Leucopenia (10,11,12,13,14,15)	0-67%	Yes	No
Hemoglobin <10gm% (10,11,13,14,15,18)	5-33%	Yes	No
Neutropenia (11,12,14,15,18)	0-33%	Yes	No
Thrombocytepenia (13,14,18)	1.5-11%	No	Yes
General			
Fever (10,11,12,13,14,15,16,17,18)	54-100%	No	Yes
Headache (10,12,13,14,16,17,18)	27-67%	No	No
Lethargy (10,13,14,18)	7-54%	Yes	Yes
Weakness (10,12,14)	15-73%	No	No
Weight loss (11,12,14)	19-100%	Yes	No
Effect on height (12,14)	70-73%	No	No
Chills (10,14)	16-21%	No	No
Lymphadenopathy (10)	6%	No	No
Bleeding (11)	9%	No	No
Gastrointestinal			
Anorexia (10,12,13,14,17,18)	8-76%	No	No
Vomiting/nausea (10,12,13,14,16,18)	13-45%	Yes	No
Abdominal pain (10,12,13,14,18)	5-43%	N o	No
Diarrhoea (10,18)	3-14%	Yes	No
Hepatitis (16,18)	1.5-14%	No	Yes
Feeling of dry mouth (10)	13%	No	No
Pain in gingiva (10)	6%	No	No
Stomatitis (13)	8%	No	No
Constipation (12)	10%	No	No
Nervous System			
Irritability (10,12,13,14,16,17,18)	8-34%	No	No
Sleep disturbance (13,14,15,17,18)	3-27%	No	No
Apathy (10,12,13)	5-23%	No	No
Drowsiness (10,15)	15-58%	No	No

Depression (11,14)	2-20%	Yes	No
Dizziness (10,14)	9-14%	No	No
Psychiatric adverse effects (14)	28%	No	No
Suicidal attempt (17)	1%	No	Yes
Skin			
Redness at the injection site (10,12,13,14,16,17,18)	8-46%	No	No
Hair loss (10,12,13,14,18)	9-24%	No	No
Rash (10,17)	3-24%	No	No
Dry skin/dermatitis (12,18)	10-29%	No	No
Pruritus (12,18)	6-7%	Yes	No
Endocrine			
Transient high TSH or T4 (12,14,18)	11-25%	No	No
Hypothyroidism (10,13,14,15,18)	1.5-8%	No	No
Thyrotoxicosis (12,18)	1.5-7%	No	Yes
Antithyroid antibodies (12,13)	14.16%	No	No
Diabetes mellitus (15,17)	2-8%	No	Yes
Other			
Pain in joints (10,12,14,17,18)	3-45%	No	No
Muscle pain (10,14,18)	9-35%	No	No
Lumbar pain (10)	26%	No	No
Bacterial infections (18)	9%	No	No
Viral infections (18)	14%	No	No
Upper respiratory infections (12)	53%	No	No
Gastrointestinal infections (12)	30%	No	No
Skin infections (12)	13%	No	No
Cough (10)	7%	No	No
Sore throat (10,12,18)	3-40%	No	No
Chest pain (10)	3%	No	No
Cough (10)	7%	No	No
Breathlessness (18)	11%	No	No
Pulmonary hypertension in (18)	1.5%	No	No
Nose bleed (12)	10%	No	No
Enuresis-dysuria (18)	3%	No	No
Palpitations (18)	3%	No	No
Reversible eye problems (17)	4%	No	No
Pain in the eye bulbs (10)	3%	No	No
Autoantobodies ANA (12)	23%	No	No
Increased Triglycerides (16)	1%	No	Yes

Table-III. Peginterferon ± ribavirin and adverse effects
Drug dose modification means either reduction in the dose or temporary stoppage*
*Drug stopped** means permanent withdrawal of the drug*

mild lymphopenia, hyperuricemia, itching, rash, cough and nasal stuffiness[9]. Since in most of the studies (except in some cases in the study by Schwarz et al 2008) used both peginterferon and ribavirin it iis difficult to differentiate the contribution of each drugs for the side effects mentioned in table-III. It is known to be teratogenic[23] and thus it is imperative for persons who receive the drug to use strict contraceptive methods both during treatment and for a period of 6 months thereafter.

THE ROLE OF LIVER BIOPSY IN THE INITIATION OF TREATMENT

The role and utility of liver biopsy in the initiation of

treatment of hepatitis C cases is still debatable, and no definite consensus exists in any guideline. The treatment may be started without liver biopsy[13,17].

CONCLUSIONS

Peginterferon α-2b and peginterferon α-2a in combination with ribavirin may be used in children above two years of age having chronic hepatitis C but is not indicated in every case. The therapy is not free from side effects as in adults.

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AUTHOR(S):

1. **DR. ABDUL REHMAN**
   MBBS, DCH, FCPS
   Assistant Professor of Paediatrics,
   Quaid-e-Azam Medical College, Bahawalpur.

Correspondence Address:
Dr. Abdul Rehman
Assistant Professor of Paediatrics,
Quaid-e-Azam Medical College, Bahawalpur.
drarehman100@yahoo.com

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