Treatment of chronic hepatitis C in children with pegylated interferon and ribavirin : the impact of dose

Maria Tufano, Maria Pia Cicalese, Maria Immacolata Spagnuolo, Vito Terlizzi, Raffaele Iorio[1]

(1) Pediatric Liver Unit, Department of Translational Medical Science, University Federico II of Naples, Naples, Italy.

Abstract

Introduction : **In the last years children with chronic hepatitis C (CHC) have been treated with Pegylated Interferon α (PEG-IFNα) and ribavirin (RBV). Treatment can cause several side effects that require reduction or interruption of therapy. The relationship between dose of PEG-IFNα and response to therapy has not been clearly evaluated. Aim of this study was to evaluate the impact of the dose of PEG-IFNα2b and RBV on the efficacy of therapy.**

Patients and method : **All children with CHC treated with PEG-IFNα2b and RBV, observed at the Paediatric Liver Unit of University Federico II of Naples from 1996 to 2006 were evaluated.**

Results : **Sixteen children with CHC treated with combined therapy were enrolled. Seven out of 16 patients (43.7%) achieved rapid virological response ; 13/16 patients (81.2%) achieved early virological response ; 5/16 patients (31.25%) relapsed ; 1 patient resulted non responder. According to percentage of expected dose, our patients were divided into two groups : the first group included 7 patients that performed an overall dosage of PEG-IFNα2b ≥ 75% of the scheduled full dose ; the second group included 9 patients that performedm PEG-IFNα2b dose < 75% of scheduled full dose. No difference was noted in terms of sustained virological response.**

Conclusion : **Modifications of therapy due to PEG-IFNα-related adverse events are frequent in children with CHC, but dose adjustments do not seem to impair efficacy of therapy.** (Acta gastroenterol. belg., **2015**, 78, **8-11**).

Key words : hepatitis C virus, Pegylated Interferon α, children.

Abbreviations : CHC, chronic hepatitis C ; PEG-IFNα, Pegylated Interferon α ; RBV, ribavirin ; SVR, sustained virological response ; G, genotype ; RVR, Rapid Virological Response ; EVR, Early Virological Response.

Introduction

Treatment of chronic hepatitis C (CHC) infected adult patients with Pegylated Interferon α (PEG-IFNα) and ribavirin (RBV), at the current standard of care, results in successful outcomes (1).

In paediatric population, CHC seems to be a milder disease with a more favourable natural course, if compared to adults (2-4). Nevertheless, cases of children with CHC who developed compensated cirrhosis in the first decade of life or required liver transplantation have been reported (5). In the largest paediatric observational study, including children with CHC infected by vertical transmission and with parenteral sources of contagion, only few (8%) spontaneously cleared viremia (6). The persistent viral replication led to end-stage liver disease in a small subgroup of patients (1.8%) characterized by perinatal exposure, maternal drug use and infection with HCV genotype (G) 1a (6).

Despite the indolent course in the majority of cases, in the last years a substantial number of children with CHC and risk features for severe disease have been treated with interferon (7) or, more recently, with combined therapy with PEG-IFNα and RBV (8,9). Furthermore, treatment may be justified because it allows definitive viral clearance in a subgroup of patients (8,9).

In children, the combined therapy can lead to a sustained virological response (SVR) and factors predictive of a higher virological response to treatment include HCV G 2 and 3 (typically > 80% SVR) and a lower viral load in those with genotype 1 (8,9). Treatment can cause several side effects that require reduction of dosage or interruption of therapy (8-10).

The relationship between the total amount of PEG-IFNα and RBV administered to the patient during the entire therapeutic cycle and response to therapy has not been clearly evaluated. Aim of this study was to evaluate, in a retrospective monocentric observational study of children with CHC treated with combined therapy, whether dose reduction of PEG-IFNα2b and RBV because of side effects had an impact on the efficacy of therapy.

Patients and methods

All children with CHC treated with PEG-IFNα2b and RBV, observed at the Paediatric Liver Unit of University Federico II of Naples from 1996 to 2006, were retrospectively evaluated.

Treatment

Treatment consisted of PEG-IFN α-2b 1.5 ug/kg of body weight once-weekly and RBV (15 mg/kg/day). Patients with G1 were assigned to 48 weeks of treatment while patients with G2, G3 and G4 were assigned to 24 weeks of treatment. Irrespective of genotype, patients

Correspondence to : Raffaele Iorio, M.D., Pediatric Liver Unit, Department of Translational Medical Science, University Federico II of Naples, Via S. Pansini 5, 80131 Naples, Italy. E-mail : riorio@unina.it

Submission date : 16/10/2014
Acceptance date : 19/09/2014

Table 1. — **Schedule for management of laboratory side effects due to therapy with pegylated Interferon α and ribavirin**

Laboratory Parameters	Reduction of PEG-INF dose to 1 ug/kg/week	Reduction of ribavirin dose to 12 mg/kg/day	Transient discontinuation
Neutrophils	< 1,500/mm^3	N/A	< 500/mm^3
Platelets	< 75,000/mm^3	N/A	< 50,000/mm^3
Creatinine	N/A	N/A	> 2 mg/dL
Hemoglobin	N/A	8.5 to < 10 g/dL	< 8.5 g/dL

with < 2 $\log_{10}$ drop in HCV-RNA at week 12 or detectable HCV-RNA at week 24 discontinued treatment.

The overall median follow up after stopping treatment was 20 months (range 8-43 months).

The treatment schedule provided indications for dose reduction or discontinuation of therapy as reported in Table 1.

Psychiatric disorders such as major depression or suicidal ideations also required therapy interruption, while irritability, agitation, aggression, mood alteration, anxiety, and affective lability did not, as elsewhere reported (8).

At baseline, and at week 2,4,8,12,24 all patients underwent physical examination and were investigated for clinical signs of liver disease. Furthermore, the following parameters were evaluated : blood cell count, liver function tests, serology for HAV, HBV and HIV, α-fetoprotein level, betaHCG (for fertile girls), HCV PCR, serum immunoglobulin level and non-organ-specific autoantibody, such as antinuclear antibodies, anti-smooth muscle antibodies, and antiliver/ kidney microsomal type 1 antibodies. For G1, the evaluation was also performed at 36 and 48 weeks.

HCV viral genotyping was performed using in vitro reverse transcription-polymerase chain reaction assay.

In all patients, modality of transmission of HCV infection and age at the time of infection were also evaluated.

Liver biopsies were performed in all patients before treatment and liver parenchyma scored with regard to hepatitis activity (graded 0-18) and fibrotic changes (staged 0-6), according to Ishak scoring system (11).

Informed consent was obtained from parents or legal guardians.

The response to therapy was classified as :

- Rapid Virological Response (RVR) defined as serum HCV RNA undetectable (< 600 IU/ml, real time PCR) after 4 weeks of treatment ;
- Early Virological Response (EVR) defined as serum HCV RNA either undetectable or decreased by ≥ 2 $\log_{10}$ after 12 weeks of treatment ;
- SVR defined as undetectable HCV RNA (< 600 IU/ml, real time PCR) at week 24 after treatment ;
- Patients were defined relapsers if, after a virological response, presented viral replication in the 12 weeks after the interruption of therapy ;
- Patients were defined non responders if presented with an active viral replication during therapy.

Exclusion criteria for treatment included decompensated liver disease, coexisting HIV or hepatitis B virus infection, hemoglobinopathy, haemophilia, malignant or immunologic diseases, preexisting neurologic or psychiatric disorder, retinopathy, substance abuse, chronic cardiopulmonary disease, and immunosuppressive treatment.

Statistical Analysis

All data are expressed as medians and ranges. Comparison of categorical variables was performed using the x^2 test. A P value of < 0.05 was considered statistically significant. Regarding the role of several variables on response to treatment (G, viral load, age in month, dosage of PEG-IFN α2b) multivariate analysis was performed.

Results

Sixteen children with CHC treated with combined therapy were enrolled.

Clinical, laboratory and histological characteristics before treatment are presented in Table 2.

The median duration of infection in patients with transfusion acquired hepatitis C was 9 years (range 5-10 years).

One patient resulted non responder. Seven out of the remaining 15 patients (46.6%) achieved rapid virological response ; 8/15 patients (53%) achieved early virological response ; 5/15 patients (33.3%) relapsed. Among the 6 patients relapser or not responder 5 were G1.

Flu-like syndrome appeared in all children. Other frequent adverse effects were fatigue, leg pain, alopecia, mild anxiety or irritability, but these events did not require reduction of dosage. The majority of patients, 14/16 (87.5%), developed more than one adverse effect. Adverse events came out most frequently during the first month of therapy. Median time for the first dosage reduction was 2.31 months.

No patient showed severe adverse effects that required therapy discontinuation. None of the patients needed a reduction of RBV dosage. On the other hand, only 2 patients (12.5%) received the entire scheduled full dose of PEG-IFNα2b. In the other 14 patients (87.5%) PEG-IFNα2b dosage was reduced because of neutropenia and immediately restored to full dose once neutrophil counts exceeded 1,500 cells/mL. No patient showed neutropenia

Table 2. — **Characteristics of 16 Children with Chronic Hepatitis C treated with combined therapy**

Patient	Sex	Age (years)	HCV Exposure	HCV genotype	Baseline viral load ($\times 10^3$ IU/mL)	Baseline ALT U/I	Staging*	Grading*	Total dosage of PEG-INFα2b (%)	Adverse effect	Response to therapy
1	M	12	Transfusion	1b	850	63	2	3	82,2	FLS, N	EVR,SVR
2	F	15	Transfusion	4c/4d	220	13	2	2	70,8	FLS, N	RVR,SVR
3	F	15	Vertical	2a/2c	30.5	54	1	2	100	FLS	RVR,SVR
4	M	16	Transfusion	1b	760	64	2	5	31,2	FLS, N	EVR, R
5	M	17	Vertical	1b	850	22	1	3	81,2	FLS, N	EVR,R
6	M	15	Transfusion	1b	425	40	2	7	36,4	FLS, N	NR
7	F	12	Vertical	2a/2c	210	17	2	6	66.6	FLS, N	RVR,SVR
8	F	14	Trasfusion	2a/2c	520	45	2	2	68.3	FLS, N	EVR, SVR
9	M	12	Trasfusion	1b	850	76	1	2	75	FLS, N, LP	EVR,R
10	M	16	Unknown	2a/2c	51	21	2	3	72.9	FLS, N	RVR,SVR
11	F	17	Transfusion	1b	850	62	3	8	63.5	FLS, N	EVR,R
12	M	12	Transfusion	2a/2c	850	37	1	2	85.4	FLS, N, A, AL	EVR, SVR
13	M	16	Transfusion	2a/2c	180	60	2	5	100	FLS, A	RVR,R
14	M	16	Unknown	1b	260	54	3	1	72.9	FLS, N	EVR,SVR
15	M	18	Transfusion	1b	130	17	2	6	92.9	FLS, N	RVR, SVR
16	M	18	Transfusion	3a	452	60	1	5	71.8	FLS, N	RVR,SVR

A, Anxiety ; AL, alopecia ; F, female ; FLS, Flu-like syndrome ; LP, leg pain ; M, male ; N, neutropenia ; NR, non responder ; PEG-INFα2b, Pegylated Interferon α ; R, relapser ; SVR, Sustained Virological Response ; RVR, Rapid Virological Response ; EVR, Early Virological Response.
* according to Ishak scoring system.

one more time. The median dose of PEG-IFNα2b received by the patients was 73.1% of the scheduled dose.

According to the percentage of the dose received with respect to the scheduled full dose, our patients were divided into two groups : the first group included 7 patients that received, at the end of therapy, an overall dose of PEG-IFNα2b ≥75% of the scheduled full dose (Group 1) ; the second group included 9 patients that received, at the end of therapy, PEG-IFNα2b dose < 75% of scheduled full dose (Group 2).

The groups were comparable for age at start of therapy, duration of HCV infection, viral load, ALT levels, histological parameters, sex and genotype (P = NS).

No statistical differences were noted in term of response to therapy : 4/7 (57.1%) patients in Group 1 achieved EVR vs 4/9 (44.4%) in group 2 (P = 0.61) ; 3/7 (42.8%) in Group 1 achieved RVR vs 4/9 (44.4%) in group 2 (P = 0.94) ; 4/7 (57%) patients included in the Group 1 and 6/9 (66.6%) patient included in Group 2 achieved SVR (P = 0.69) ; 3/7 (42.8%) patients in Group 1 relapsed vs 2/9 (22.2%) patients in Group 2 (P = 0.37). Only one patient with G1 (patient 6) in Group 2 resulted non responder so he discontinued therapy after 24 weeks ; due to IFN-induced neutropenia he received a total amount of Peg-IFN of 36.4% of the scheduled dose for 6 months.

Overall, patients who achieved SVR received a median dosage of PEG-IFNα2b of 78.3% (range 68.3-100%) of the scheduled dose. Patients who did not achieved SVR received a median dose of 64.5% (range 31.25-100%) ; there was not a statistically significant difference regarding percentage of total dose received between patients who achieved SVR and those without SVR (P = 0.278).

The percentage of the dose received of PEG-IFNα2b was 82.2 ± 5.7% (range 72.9-92.9) in 3 patients with genotype 1b and SVR and 63.5 ± 10.1% (range 31.2-81.2) in 5 patients with the same genotype but without SVR (P : NS).

Discussion

Combination therapy of PEG-IFN α-2a or α-2b with RBV is standard of care for adults with CHC (1). In children and adolescents, PEG-IFN treatment in combination with RBV produces a SVR rate in adequately treated individuals (8,9). Thus, this option can be offered to all paediatric patients, beyond three years of life, regardless of the level of aminotransferases or modality of infection (8,9).

The majority of treated children and adolescents tolerate combined therapy even if almost all patients experience at least one side effect (8-10,12).

Most adverse events are mild to moderate, such as flu-like symptoms including fever, anorexia, fatigue, dry skin and moderate hair loss. Bone marrow suppression induced by IFN-α, characterized by the decreased levels of total white blood cell and absolute neutrophil counts, and, to a lesser extent, platelets and red blood cells, is the next most common toxicity sign after constitutional

symptoms (9,10). On the other hand, RBV is the main contributor to the onset of haemolytic anaemia. Dose adjustments may be insufficient to resolve marrow suppression, and interventions to treat severe or symptomatic anaemia or neutropaenia may be necessary (8). Available agents include epoetin alfa, for anaemia, granulocyte colony stimulating factor for neutropaenia, and blood products. This adjuvant therapy has been documented to enhance compliance to treatment regimens, improve rates of SVR, and improve quality of life, but currently it is not approved for children in the context of therapy for CHC (8).

Furthermore, despite significant advances in the therapies available for treating HCV infection in adults, in particular with direct-acting antivirals (DAA), little data are available on the use of these emerging therapies for CHC in children. Indeed preliminary data from investigational studies suggest the potential for cure rates of 80%-90% in G1 infection using combinations of DAAs and RBV without PEG-IFN, but larger studies will be needed to confirm these results across a wider range of populations (13).

Therefore in children with CHC combined therapy with PEG-INF and RBV may be the only chance to eradicate viral infection. Unfortunately, in some patients as a consequence of therapy-induced side effects, either dosage reduction or interruption of therapy are sometimes required (8-10,12,14). At the present, the real the impact of dosage reduction of PEG-IFNα2b and/or RBV on SVR is not well clarified (9,10).

This study, investigating the relationship between modifications of PEG-IFNα2b dosage due to side effects and response to therapy in children with CHC, confirms that PEG-IFNα2b resulted effective even if lower doses were used in consequence of side effects. Indeed, in our series also when dose of PEG-IFNα2b was reduced by a third, the effectiveness of therapy remained unchanged. Patients treated with lower doses of PEG-IFNα2b for the control of side effects showed the same percentage of SVR.

In the present study no relationship was found between duration of HCV infection and response to therapy both in vertically and in post-transfusion HCV-infected patients.

It is to note that the most of the non responders and relapsers are G1 as elsewhere reported (1-4,14).

As for RBV-induced haemolytic anemia, that is the main adverse event of this drug, in any of the studied patient RBV dose changes were required.

In conclusion, modifications of therapy due to PEG-IFNα-related adverse events are frequent in children with CHC, but dose adjustments do not seem to impair efficacy of therapy.

Aware of the small number of our cohort we believe that further and larger studies are needed to evaluate the impact of the dose of the drugs, in consequence of side effects, on the efficacy of therapy in children with CHC.

References

1. GHANY M.G., STRADER D.B., THOMAS D.L., SEEFF L.B. American Association for the Study of Liver Diseases : Diagnosis, management, and treatment of hepatitis C : an update. *Hepatology*, 2009, **49** : 1335-74.
2. CASIRAGHI M.A., DE PASCHALE M., ROMANÒ L., BIFFI R., ASSI A., BINELLI G. *et al*. Long-term outcome (35 years) of hepatitis C after acquisition of infection through mini transfusions of blood given at birth. *Hepatology*, 2004, **39** : 90-6.
3. IORIO R., GIANNATTASIO A., SEPE A., TERRACCIANO L.M., VECCHIONE R., VEGNENTE A. Chronic hepatitis C in childhood : an 18-year experience. *Clin. Infect. Dis*., 2005, **41** : 1431-7.
4. JARA P., RESTI M., HIERRO L., GIACCHINO R., BARBERA C., ZANCAN L. *et al*. Chronic hepatitis C virus infection in childhood : clinical patterns and evolution in 224 white children. *Clin. Infect. Dis*., 2003, **36** : 275-80.
5. ZANCAN L., STRAFELLA MS., BRUGIOLO A., MALUSA T., D'AMORE E. Chronic hepatitis C virus infection in childhood and early cirrhosis : it is possible ? *J. Pediatr. Gastroenterol. Nutr*., 2000, **30** : 350-1.
6. BORTOLOTTI F., VERUCCHI G., CAMMÀ C., CABIBBO G., ZANCAN L., INDOLFI G. *et al*. Long-term course of chronic hepatitis C in children : from viral clearance to end-stage liver disease. *Gastroenterology*, 2008, **134** : 1900-7.
7. JACOBSON K.R., MURRAY K., ZELLOS A., SCHWARZ K.B. An analysis of published trials of interferon monotherapy in children with chronic hepatitis C. *J. Pediatr. Gastroenterol. Nutr*., 2002, **34** : 52
8. MACK C.L., GONZALEZ-PERALTA R.P., GUPTA N., LEUNG D., NARKEWICZ M.R., ROBERTS E.A. *et al*. NASPGHAN practice guidelines : Diagnosis and management of hepatitis C infection in infants, children, and adolescents. *J. Pediatr. Gastroenterol. Nutr*., 2012, **54** : 838-55.
9. WIRTH S. Current treatment options and response rates in children with chronic hepatitis C. *World J. Gastroenterol*., 2012, **18** : 99-104.
10. RIDRUEJO E., ADROVER R., COCOZZELLA D., FERNÁNDEZ N., REGGIARDO M.V. Efficacy, tolerability and safety in the treatment of chronic hepatitis C with combination of PEG-Interferon – Ribavirin in daily practice. *Ann. Hepatol*., 2010, **9** : 46-51.
11. KNODELL R.G., ISHAK K.G., BLACK W.C., CHEN T.S., CRAIG R., KAPLOWITZ N. *et al*. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology*, 1981, **1** : 431-435.
12. SCHWARZ K.B., GONZALEZ-PERALTA R.P., MURRAY K.F., MOLLESTON J.P., HABER B.A., JONAS M.M. *et al*. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. *Gastroenterology*, 2011, **140** : 450-458.
13. EL-SHABRAWI M.H., KAMAL N.M. Burden of pediatric hepatitis C. *World J. Gastroenterol*., 2013, **19** : 7880-7888.
14. WIRTH S., RIBES-KONINCKX C., CALZADO M.A., BORTOLOTTI F., ZANCAN L., JARA P. *et al*. High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. *J. Hepatol*., 2010, **52** : 501-7.