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Pegylated interferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C genotype 4 in adolescents

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ABSTRACT

Background. Hepatitis C is endemic in the Middle East where genotype 4 accounts for most cases. Data regarding the safety and efficacy of peginterferon plus ribavirin for the treatment of chronic hepatitis C in children and adolescents, particularly those infected with genotype 4 is limited. **Aim.** To evaluate the efficacy and tolerability of peginterferon alfa-2b in combination with ribavirin in adolescents chronically infected with HCV genotype 4. **Patients and methods.** In an open-labeled, uncontrolled pilot study, 12 adolescents (range14-17 years) were treated with subcutaneous peginterferon alfa-2b at a dose of 1.5 mg/kg body weight once per week plus oral ribavirin (15 mg/kg/day) for 48 weeks. Patients were followed for 24 weeks post-treatment. All patients had biopsy proven hepatitis without cirrhosis. **Results.** One patient withdrew from the study due to developing insulin dependent diabetes mellitus 4 months into treatment. The remaining patients received at least 80% of the prescribed dose of pegylated interferon and ribavirin. Sustained viral response was observed in 9 patients (75%). The most frequent side effect was flu like illness which was reported in all patients. Sixty seven percent had leucopenia, but only one individual required adjuvant therapy with hematologic growth factor. Four patients had anemia requiring ribavirin dose reduction. One patient developed hypothyroidism. **Conclusion.** Combination treatment of peginterferon alfa-2b with ribavirin appears to be efficacious and relatively safe in adolescents with chronic hepatitis C genotype 4.B.

Key words. Chronic hepatitis C virus. Genotype 4. Adolescents. Peginterferon alpha-2b.

INTRODUCTION

Hepatitis C Virus (HCV) is a major cause of liver disease in the Middle East where, in some population, the prevalence rate reaches 15-20%.[1-3] In chronically infected adults, 20% develop cirrhosis and hepatocellular carcinoma. The natural history of HCV infection in children and adolescents is less certain. In a recent multi center study from Italy 504 HCV seropositive children were followed prospectively and retrospectively.[4] Spontaneous viral clearance was observed in only 8% of the patients, most of whom were infected with HCV genotype 3. Another concerning observation was that 1.8% of the reported children progressed to decompensated cirrhosis. Risk factors associated with progression included perinatal acquisition of the virus and comorbid conditions such as thalassemia.[5,6] These observations and the fact that infected children represent a reservoir for infection and may suffer from the social stigma associated with infection, have prompted a number of therapeutic trials using non-pegylated interferon alone or in combination with ribavirin.[7-9] Most of these trials were small. Similarly data regarding the efficacy and safety of pegylated interferon alone or plus ribavirin in children and adolescent are very limited.[10-13] Moreover, the studies were carried out in Western communities where HCV genotype 1 is the predominant variant followed by genotype 2/3 and may not generalized to the Gulf states where genotype 4 is endemic and where demographic differences may affect anti-viral response.

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The aim of this pilot study was to determine the efficacy and safety of pegylated interferon alfa-2b plus weight based ribavirin combination therapy in adolescents infected with HCV genotype 4.

PATIENTS AND METHODS

Patients selection

Treatment-naive patients, aged 14 to 17 years, with detectable HCV RNA, genotype 4 and anti-HCV positive liver biopsy findings consistent with the diagnosis of chronic hepatitis C were eligible for study participation. The patients were seen by their physicians and the decision to treat was a decision made by both physician and patient/patient's family on clinical grounds. They study included only those patients for whom a decision to treat was made. The patients were excluded if there was clinical or biochemical evidence of hepatic decompensation, severe psychiatric disorders, hemoglobin < 100 g/L, white blood cell count < 2,500/mm^3, platelet counts <70,000/mm^3, and serum creatinine level > 200 mmol/L. Informed consent was obtained from all patients and their parents prior to study enrollment in accordance with the ethical code of our institution. This study was approved by our institutional ethical review board.

Study design and efficacy end points

Twelve children and adolescents (8 males) with chronic HCV were included in an open-label uncontrolled pilot study (Figure 1). The patients were included independent of mode of acquisition of infection, level of serum aminotransaminases, or serum HCV RNA viral load. All patients received subcutaneous peginterferon alfa-2b at a dose of 1.5 g/kg body weight once per week plus rebavirin (15 mg/kg/day) (Pegatron, Schering-Plough Inc) for 48 weeks. The primary efficacy end point was sustained virological response (SVR), defined as an undetectable (< 50 IU/mL) HCV RNA after 24 weeks of treatment-free follow-up (week 72), Secondary end points include early virologic response (EVR), defined as HCV RNA < 50 IU/mL at week 12 of therapy, and end-of-treatment response (ETR), defined as HCV RNA < 50 IU/Ml at week 48.

Serum HCV RNA testing was performed using a qualitative polymerase chain reaction assay (COBAS AMPLICOR HCV TEST V 2.0, Roche Diagnostics) A liver biopsy was performed on all patients pre-treatment and the METAVIR scoring system was used to grade liver histology. All mothers were tested for anti-HCV antibodies.

Safety assessments

The clinical and laboratory data as well as adverse effects were evaluated and reviewed, with the completion of case report forms, at weeks 1, 2, 4, 6, 8, and 12 and monthly thereafter, Stepwise reductions in peginterferon alfa-2b or ribavirin dose were permitted for management of adverse events and laboratory abnormalities. Hematologic growth factors were allowed when indicated, for clinically significant anemia or neutropenia at the discretion of the study investigators.

Compliance monitoring

In all patients, peginterferon alfa-2b was administered in the local primary care clinic by a registered nurse who documented compliance. Adherence to ribavirin ingestion was monitored by capsule count.

RESULTS

Of 12 children and adolescents (Table 1), 11 completed the study. On pre-treatment liver biopsy, all

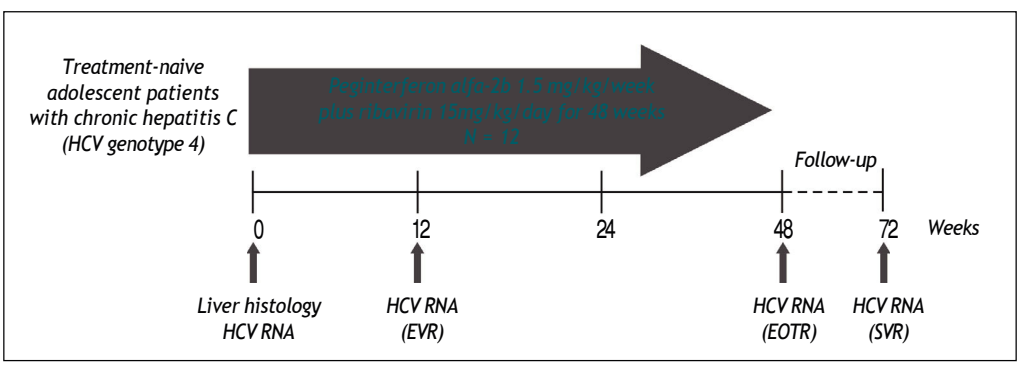

Figure 1. Study design.

Table 1. Baseline characteristics.

Characteristic	Patients (N = 12)
Age, y, mean (range)	15.75 (14-17)
ALT (UI/L), mean (range)	91 (34-194)
Histologic grade, mean (range)*	1.67 (1-2)
Fibrosis score, mean (range)*	0.67 (0-3)
HCV RNA x 10^6 IU/Ml, mean (range)	078025 (0.23-1.8)
Risk factor, n (%)	
Dental procedures	2 (17)
Trnasfusion	1 (8)
IV drug use	2 (17)
Vertical transmission	2 (17)
Unknown	5 (42)

*METAVIR scoring system; ALT: alanine transferase; IV: intravenous.

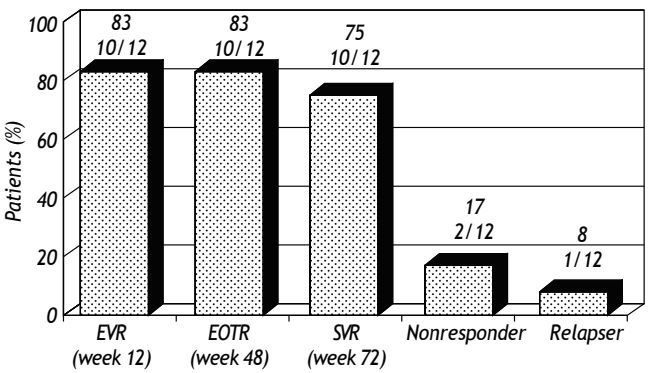

***Figure 2**. Response to therapy.*

patients had histology features of active hepatitis without cirrhosis, Mean age at diagnoses was 15.75 years (range 14-17 years), the alanine aminotransferase (ALT) values were abnormal in 10 patients (83%), with a mean of 91 IU/L (range: 34-194 IU/L). HCV RNA was detected in the baseline sera of all patients with a median level of 0.78 x 10^6 IU/ml (range: 0.23-1.8 x 10^6) One patient withdrew from study after 4 months because of the development of type 1 diabetes mellitus. All remaining patients took at least 80% of the peginterferon alfa-2b and ribavirin. Early virologic response (EVR) and end-of-treatment response (ETR) were achieved in 10 (83%) of 12 patients, and sustained virologic response was achieved in 9 (75%) of 12 patients (Figure 2). All patients who achieved an SVR also achieved an EVR. Two patients were nonresponders, one patient achieved an ETR and then relapsed during the third month of follow up. The two nonresponders had baseline HCV RNA levels that were higher than those of most other patients (1.1 x 10^6 IU/ML and 1.8 x 10^6 IU/ML).

Table 2. Treatment-emergent events.

Adverse event	Incidence (%)
Fever	12 (100)
Myalgia	7 (58)
Insomnia	1 (8)
Hipothyroidism	1 (8)
Type 1 diabetes mellitus	1 (8)
Anemia < 10 g/L	4 (33)
Nautropenia	2 (17)

Route of acquisition of infection

Of 12 patients, 2 (17%) had extensive dental procedures, 2 (17%) gave history of parenteral drug use, 2 (17%) were born to mothers infected with HCV raising the suspicion of vertical transmission, and 1 (8%) had multiple blood transfusions. The rest (42%) did not have an identifiable risk factor for HCV.

Adverse effects of treatment

Flu-like symptoms were the most common adverse event and all patients experienced fever (Table 2). Sixty-seven percent of the patients had leucopenia, but only 1 patient required treatment with growth factors. Anemia developed in 4 patients, 3 of them were females. They all had coincidental menorrhagia. The dose of ribavirin of these patients was reduced when hemoglobin was below 10 gm/dL.

DISCUSSION

The combination of pegylated interferon alfa and ribavirin is currently the standard therapy for chronic hepatitis C infection in adults. Sustained virologic response is achieved in 44-75% of patients depending on genotype.[14-18] The single most important determinant of treatment response is viral genotype, such that 45-50% of patients infected with HCV genotype 1 experience an SVR compared to 75% of those infected with genotypes 2 and 3. Data regarding the efficiency of pegylated interferon plus ribavirin combination therapy in genotype 4 infected patients are limited because most of the large registration trials were conducted in western countries where HCV genotype 4 is relatively uncommon and some trials may have excluded genotype 4. In the Middle East, however, most HCV infections are caused by the genotype 4 variant. Pegylated interferon plus ribivarin therapy has been reported to be associated with a SVR of 68% in adults infected with this genotype.[14,15]

In children and adolescents infected with HCV data regarding antiviral therapy are very limited and almost non-existent for genotype 4 patients. Standard non-pegylated interferon monotherapy was associated with an SVR in 33-45% of patients.[6,19,20] With the use of standard non-pegylated interferon plus ribavirin combination in children and adolescents. The SVR rate varied from 41-61%[8,21-25] depending on HCV genotype.

With regards to the current gold-standard therapy of peginterferon and ribavirin which has only recently recently approved by United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for a healthy children over three years of age,[26] there are only a few published reports regarding its efficacy and safety in children and adolescent with chronic hepatitis C. In an open-labeled uncontrolled trial from Germany 62 children and adolescents were treated with peginterferon alfa-2b and ribavirin for 48 weeks.[11] The overall SVR was 58%.

The mode of transmission appeared to influence treatment outcome. SVR was achieved in 70% and 48% of patients who acquired HCV through parenteral exposure, or by vertical transmission respectively. But, as in adults, HCV genotype was the main determinant of response. The rate of SVR among patients with genotype 1 was 47%, compared to 100% in patients infected with genotypes 2 and 3. The study included only 2 children with genotype 4, one of whom had a SVR. However, in a recent global, multicenter, open-label study, where 107 children and adolescents enrolled and treated with combination therapy, the overall SVR was achieved by 65% of all patients, genotype was the main predictor of response with 53%, 93 and 80% in patients infected with G1, G2/3 and G4, respectively.[13] To date we could not find published reports regarding the efficacy and safety of pegylated interferon and ribavirin in adolescents infected with HCV genotype 4. The SVR, in our study, was comparable to what we had observed in adults.[1,2] In our study it is important to note that nine patients with EVR had SVR and more importantly that the two patients without EVR had no SVR. The small number of patients included in this study limits the analyses but this data suggests that stopping therapy in those without response after 12 weeks of treatment is appropriate for HCV type 4. A number of factors might have contributed to the relatively high response rate. Most patients had mild liver disease, but most importantly low pre-treatment viral load. Furthermore, compliance was excellent, because patients and parents were counseled extensively, more importantly compared to the western culture, Arab adolescents comply with family traditions for abiding to their parents' wishes. A relatively high dose of ribavirin (15 mg/kg) was used. The latter has been shown to induce better SVR.[6] The cause for extending therapy for 48 weeks is that the value of early virologic response as a predictor of SVR was not well established in children. Moreover, at the time, there was evidence in adults that non-responders may benefit from interferon therapy in terms of histologic activity. Also, per protocol, we wanted the entire group to receive the same drug regimen for uniformity. Finally, most of our patients had presumed parenterally acquired disease.

CONCLUSION

This small open label pilot study shows that pegylated interferon plus ribavirin appear to be effective and relatively safe for the treatment of HCV genotype 4 in adolescent and children. Treating this population, therefore, may be appropriate. However, larger controlled trials are needed to confirm our findings.

ABREVIATIONS

- **HCV:** Hepatitis C virus.
- **Anti-HCV:** Antibody to hepatitis C virus.
- **ALT:** Alanine aminotransferase.
- **SVR:** Sustained virological response.
- **EVR:** Early virological response.
- **ETR:** End-of-treatment response.
- **IVDU:** Intravenous drug user.
- **HCV RNA:** Hepatitis C ribonucleic acid.

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REFERENCES

1. Abdel-Aziz F, Habib M, Mohamed MK, Abdel-Hamid M, Gamil F, Madkour S, Mikhail NN, et al. Hepatitis C virus (HCV) infection in a community in the Nile Delta: population description and HCV prevalence. *Hepatology* 2000; 32: 111-5.
2. Ray SC, Arthur RR, Carella A, Bukh J, Thomas DL. Genetic epidemiology of hepatitis C virus throughout Egypt. *J Infect Dis* 2000; 182: 698-707.
3. Angelico M, Renganathan E, Gandin C, Fathy M, Profili MC, Refai W, De Santis A, Nagi A, et al. Chronic liver disease in

the Alexandria governorate, Egypt, contribution of schistosomiasis and hepatitis virus infections. *J Hepatololgy* 1997; 26: 236-43.
4. Bortolotti F, Verucchi G, Cammà C, Cabibbo G, Zancan L, Indolfi G, Giacchino R, et al. Italian Observatory for HCV Infection and Hepatitis C in Children. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterology* 2008; 134: 1900-7.
5. Lai ME, De Virgilis S, Argiolu F, Farci P, Mazzoleni AP, Lisci V, Rapicetta M, et al. Evaluation of antibodies to hepatitis C virus in a long-term prospective study of posttransfusion hepatitis among thalassemic children: comparison between first-and second-generation assay. *J Pediatr Gastroenterol Nutr* 1993; 16: 458-64.
6. Jonas MM. Children with hepatitis C. *Hepatology* 2002; 36: S173-8.
7. González-Peralta RP, Kelly DA, Haber B, Molleston J, Murray KF, Jonas MM, Shelton M, et al. International Pediatric Hepatitis C Therapy Group. Interferon alfa-2b in combination with ribavirin for the treatment of chronic hepatitis C in children: efficacy, safety, and pharmacokinetics. *Hepatology* 2005; 42: 1010-8.
8. Wirth S, Lang T, Gerner P, Gehring S. Interferon-alpha and ribavirin treatment in children and adolescents with chronic hepatitis C. *Hepatology* 2002; 36: 1280-4.
9. Jacobson KR, Murray K, Zellos A, Schwarz KB. An analysis of published trials of interferon monotherapy in children with chronic hepatitis C. *J Pediatr Gastroenterol Nutr* 2002 Jan; 34(1): 52-8.
10. Schwarz KB, Mohan P, Narkewicz MR, et al. Safety, efficacy and pharmacokinetics of peginterferon alpha2a (40 kd) in children with chronic hepatitis C. *J Pediatr Gastroenterol Nutr* 2006 Oct; 43(4): 499-505.
11. Wirth S, Pieper-Boustani H, Lang T, et al. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. *Hepatology* 2005; 41: 1013-18.
12. Baker RD, Dee D, Baker SS. Response to pegylated interferon alpha-2b and ribavirin in children with chronic hepatitis C. *J Clin Gastroenterol* 2007 Jan; 41(1): 111-14.
13. Wirth S, Ribes-Koninckx C, Calzado MA, et al. High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. *J Hepatol* 2010 Feb 4. In press.
14. Hassan F, Asker H, Al-Khaldi J, et al. Peginterferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C genotype 4. *Am J Gastroenterol* 2004; 99: 1733-7.
15. Kamal S, El Tawail AA, Nakano T, et al. Peginterferon alpha 2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virologic response. *Gut* 2005; 54: 858-66.
16. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975-82.
17. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001; 358: 958-65.
18. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; 140: 346-55.
19. Bortolotti F, Giacchino R, Vajro P, Barbera C, Crivellaro C, Alberti A, Nebbia G, et al. Recombinant interferon-alfa therapy in children with chronic hepatitis C. *Hepatology* 1995; 22: 1623-7.
20. Marcellini M, Kondili LA, Comparcola D, Spada E, Sartorelli MR, Palumbo M, Rapicetta M. High dosage alpha-interferon for treatment of children and young adults with chronic hepatitis C disease. *Pediatr Infect Dis J* 1997; 16: 1049-53.
21. Christensson B, Wiebe T, Akesson A, Widell A. Interferon-alfa and ribavirin treatment of hepatitis C in children with malignancy in remission. *Clin Infect Dis* 2000; 30: 585-6.
22. Lackner H, Moser A, Deutsch J, Kessler HH, Benesch M, Kerbl R, et al. Interferon-alpha and ribavirin in treating children and young adults with chronic hepatitis C after malignancy. *Pediatrics* 2000; 106: E53.
23. Kelly DA, Bunn SK, Apelian D, Baczkowski A, Gupta S, Laughlin M, et al. Safety, efficacy, and pharmacokinetics of interferon alfa-2b plus ribavirin in children with chronic hepatitis C. *Hepatology* 2001; 34: 342A.
24. Su¨oglu O¨ D, Elkabes B, So¨ku¨cu¨ S, Saner G. Does interferon and ribavirin combination therapy increase the rate of treatment response in children with hepatitis C. *J Pediatr Gastroenterol Nutr* 2002; 34: 199-206.
25. Figlerowicz M, Sluzewski W, Koala-Piaskowska A, Mozer-Lisewska I. Interferon alpha and ribavirin in the treatment of children with chronic hepatitis C. *Eur J Pediatr* 2004; 163: 265-7.
26. Jara P, Hierro L. Treatment of hepatitis C in children. *Expert Rev Gastroenterol Hepatol* 2010 Feb; 4(1): 51-61. (In press).