JOURNAL OF INTERFERON & CYTOKINE RESEARCH
Volume 36, Number 1, 2016

DOI: 10.1089/jir.2015.0066

Safety and Efficacy of Combined Treatment with Pegylated Interferon Alpha-2b and Ribavirin for HCV Genotype 4 in Children

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Combined treatment with pegylated interferon (PEG-IFN)-α2b and ribavirin (RBV) is the only currently approved treatment for hepatitis C virus (HCV) infection in children. The aim of this study was to assess the safety and efficacy of combined treatment with PEG-IFN-α2b and RBV in Egyptian children and adolescents with genotype 4 (GT4) HCV infection. The study included 66 patients (3–17 years of age), of both sexes, infected with HCV GT4, treated with PEG-IFN-α2b (60 μg/m^2), subcutaneously once weekly plus RBV (15 mg/kg/day) in 2 divided oral doses. Efficacy was assessed by achievement of sustained virological response (SVR). Safety was assessed by questionnaires directed to the patients at specific intervals, growth assessment and laboratory tests. SVR was achieved in 28 patients (42.4%). Nonresponders had significantly commoner history of treated malignancies ($P=0.03$), baseline lower absolute neutrophil count (ANC; $P=0.009$), higher gamma glutamyl transpeptidase (GGT; $P=0.003$), and higher viral load ($P=0.03$). Fever was the most frequently reported side effect occurring in 98.5% of the patients followed by musculoskeletal symptoms. Neutropenia was observed in 36 patients (54.6%) and necessitated treatment discontinuation in 1 patient. Decline in both weight and height percentiles was observed in 70% of children who received the combined therapy for a total of 48 weeks. In conclusion, the currently available treatment for HCV GT4 in pediatric patients has modest SVR with numerous adverse events necessitating meticulous monitoring to optimize care of the patients. Side effects could be managed with dose modifications and specific treatment when necessary.

Introduction

Hepatitis C virus (HCV) infection is a serious health problem worldwide that establishes a chronic infection in up to 85% of cases (Welbourn and Pause 2007). HCV genotype 4 (GT4) is responsible for ~20% of the cases of chronic HCV infection worldwide (Wantuck and others 2014). Egypt has the highest prevalence of HCV infection in the world. HCV is one of the 5 top leading causes of death in Egypt (Miller and Abu-Raddad 2010). Studies of the magnitude of HCV infection in Egyptian children revealed a prevalence of 3% in upper Egypt and 9% in lower Egypt (Kamal 2011). The main HCV GT in Egypt is GT4 (Kamal and Nasser 2008).

Treatment of chronic HCV aims at slowing disease progression, preventing complications of cirrhosis, reducing the risk of hepatocellular carcinoma, and treating extrahepatic complications of the virus (Reddy and others 2009). The percentages of patients achieving sustained virological response (SVR) significantly improved with advances in the therapeutic regimens. However, SVR rates are still below target, especially for the difficult to treat HCV GT1 and GT4 (Kamal 2014).

Despite that oral direct acting antivirals have revolutionized HCV therapy in adults interferon (IFN) plus ribavirin (RBV) are the only currently approved therapy for HCV in children and adolescents. These dramatic changes are expected to affect therapy for pediatric HCV shortly in the near future.

Combined treatment with pegylated interferon (PEG-IFN)-α2b and RBV was approved by the United States FDA in December 2008 and by the European Medicines Agency in December 2009 for children aged 3 years and older (Ghany and others 2009) and is still the only available treatment for HCV infection in children until the present time.

IFN-based regimens have moderate to severe side effects, including hematologic adverse events (neutropenia and thrombocytopenia), fatigue, irritability, fever, myalgia, arthralgia, inflammation at the injection site, and cardiac dysrhythmia, which negatively influence the tolerability and adherence of patients with therapy (Kamal 2014).

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The aim of this work was to assess the efficacy and safety of combined treatment of PEG-IFN-α2b and RBV in Egyptian children and adolescents with GT4 chronic HCV infection.

Patients and Methods

This was a prospective study conducted at the Pediatric Hepatology Unit, Cairo University Pediatric Hospital (Cairo, Egypt) from July 2010 till February 2014. The study included 66 patients of both sexes. A written informed consent was signed by their parents/guardians before starting treatment after explaining the treatment plan and possible risks. The study protocol was approved by the institutional review board and ethical committee.

Patients included were diagnosed as chronically HCV infected based upon presence of antibodies to HCV and positive HCV RNA for more than 6 months. Treatment outcome was assessed by the absence of detectable viral RNA in blood 24 weeks after end of treatment, ie, SVR.

Pre-enrollment investigations included complete blood count, liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, alkaline phosphatase (AP), GGT, serum albumin, and prothrombin time (PT)], hepatitis B surface antigen (HBsAg), random blood glucose, and glycosylated hemoglobin, if the patient was diabetic, serum creatinine, serum ferritin, antinuclear antibody, thyroid stimulating hormone (TSH), alpha-1 antitrypsin, serum ceruloplasmin, ocular examination, abdominal ultrasound, and percutaneous needle liver biopsy.

HCV antibody test was done using third generation enzyme-linked immunosorbent assay. HCV-RNA testing was performed using quantitative real-time polymerase chain reaction (PCR) on Applied Biosystems 7500 Real time PCR System using kits supplied by Qiagen [Qiagen GmbH (Hoffmann-La Roche AG), Hilden, Germany]. HCV genotyping was performed by the optimized HybProbe HCV genotype-kit according to the manufacturer protocol (TIB MOBIOL GmbH, Berlin, Germany).

Percutaneous liver biopsy was done using suction technique with core aspiration needle, Menghini needle (secure cut biopsy needle 16G; HS Hospital Service S.p.A., Aprilia [LT], Italy). Histological assessment was performed with the same experienced histopathologist. Hepatic necroinflammatory activity and liver fibrosis were evaluated according to Ishak staging and grading scores (Ishak and others 1995). Necroinflammatory activity [histological activity index (HAI)] was classified into mild (score 1–5), moderate (score 6–8), and severe (score 9–18). Fibrosis was classified into mild (stage 1), moderate (stages 2–3), and severe fibrosis or cirrhosis (stages 4–6).

The study included children aged 3 to 18 years, positive for HCV antibodies for more than 6 months with positive HCV RNA, hemoglobin level ≥10 gm/dL, ANC ≥1,500/mm^3, platelet count ≥75,000/mm^3, serum albumin >3.5 gm/dL, PT ≤3 seconds above the upper limit of normal, normal creatinine level, and normal TSH.

Patients were excluded if they had a comorbid medical condition that could compromise the tolerability of the study drugs. Exclusion criteria included body mass index (BMI) ≥95th percentiles according to Egyptian growth curves (Standard Egyptian Growth 2008); uncontrolled diabetes (Hb A1C >6.5), multitransfused patients (serum ferritin >500), decompensated cardiac disease, major central nervous system trauma or seizures requiring medications, psychiatric disorders, evidence of retinopathy, autoimmune disease, steroids or immunosuppressive therapy, substance abuse, hypersensitivity to IFN or RBV, previous IFN therapy within 1 year, decompensated liver disease (liver cell failure), and non-GT4 HCV or any associated cause of liver disease other than HCV (co-infection with HBV, alpha-1 antitrypsin deficiency, Wilson's disease, or autoimmune hepatitis).

All included patients were subjected to the following:

- Full history taking with special emphasis on history of previous treatment for malignancy, history of previous treatment for HCV.
- General and local abdominal examination for organomegaly or ascites.
- Weight, height, and BMI were plotted on Egyptian growth curves (Standard Egyptian Growth 2008).

Children who fulfilled the inclusion criteria were treated with PEG-IFN-α2b in a dose of 60 μg/m^2, given as subcutaneous injection once weekly and RBV in a dose of 15 mg/kg/day in 2 divided oral doses.

Efficacy assessment

Quantitative HCV RNA by PCR was repeated 12 weeks after starting treatment. Treatment was continued for patients who had negative HCV RNA or whose viral load decreased by more than 2 log from the basal viral load, ie, early virologic response (EVR). On week 24, HCV RNA was tested, and if positive, treatment was discontinued. For those with negative HCV RNA at 24 weeks, treatment was continued for 48 weeks when HCV RNA was retested for end of treatment response (ETR). At week 72, HCV RNA was tested to confirm the SVR, which is the primary efficacy end point of the study. Responders were labeled according to the result of SVR.

Safety assessment

To detect expected side effect of therapy, specific investigations, weight and height measurements, and questionnaires directed to the patients or parents were routinely performed at specific intervals. Complete blood count, liver functions, PT, serum creatinine and reported adverse events were done on weeks 0, 1, 2, and 4, then monthly till the end of treatment. TSH, fundus examination, weight and height measurements were done on weeks 0, 12, 24, and 48.

Information on possible adverse events was obtained, in every visit, by asking the patients in a structured way about specific, commonly observed, and expected side effects of the study medications including fever, chills, myalgias, arthralgias, headache, nausea, vomiting, anorexia, dyspepsia, itching, skin rash, cough, shortening of breath, hair loss, injection site reaction, weight loss, decreased concentration, insomnia, and depression.

Accordingly, doses of IFN or RBV were modified or discontinued (Table 1). Due to possible transient growth inhibition of IFN, evaluation of growth parameters was performed on a regular basis with recalculation of the doses accordingly.

Statistical methods

Data were collected and tabulated. Statistical Package for Social Science (SPSS) program version 17.0 was used for data analysis. Mean and standard deviation (SD) or median

Table 1. Guidelines for Dose Modification of Pegylated Interferon-α2b and Ribavirin During Treatment of Chronically HCV-Infected Children

Laboratory values	*PEG-IFN-α2b*	*Ribavirin*
Hemoglobin <10 g/dL		First reduction to 12 mg/kg/day Second reduction to 8 mg/kg/day
TLC <1,500/mm^3 Neutrophils <750/mm^3 Platelets <70,000/mm^3	First reduction to 40 mcg/m^2/week Second reduction to 20 mcg/m^2/week	No dose change
Hemoglobin <8.5 g/dL TLC <1,000/mm^3 Neutrophils <500/mm^3 Platelets <50,000/mm^3 Creatinine >2 mg/dL	Permanently discontinue	Permanently discontinue

HCV, hepatitis C virus; PEG-IFN, pegylated interferon; TLC, total leukocytic count.

and interquartile range were estimates of quantitative data including age, laboratory results, and growth parameters; while frequency and percentage were estimates of qualitative data as sex, clinical presentations, histopathological results, and treatment side effects. Comparison between responders and nonresponders in age, sex, and viral load, basic laboratory results were tested by Student's *t*-test, Mann–Whitney *U* test for quantitative data, and by Chi-square test for qualitative data. Comparing pre and post-treatment laboratory data in the responders was done for quantitative homogenous data using Student's paired *t*-test and for nonhomogenous data using Wilcoxon test and by Chi-square test for qualitative data. A 2-sided P value < 0.05 was considered statistically significant.

Results

The study included 66 children, chronically infected with HCV GT4; 43 (65.2%) were boys. Mean age of the patients (±SD) at the time of enrollment in the study was 10.9 ± 3.5 years (ranging between 3 and 17 years). The mean age at HCV diagnosis was 8.7 ± 3.8 years.

Thirteen patients (19.7%) had history of treated malignancies including lymphoma, leukemia, Wilm's tumor, and retinoblastoma. Ten patients (15.2%) had received previous unsuccessful treatment for HCV, which was stopped at least 1 year before enrollment in our study.

The mean (±SD) BMI for the patients was 18.4 (±3.9). Abdominal examination was normal in 57 patients (86.4%), while 4 patients (6.1%) had hepatomegaly, 1 patient had hepatosplenomegaly and 4 patients had scar of previous operations. Results of pre-enrollment investigations done for the patients before starting treatment are summarized in Table 2.

Abdominal ultrasound was normal in 62 patients (93.9%), 1 had hepatosplenomegaly, 3 had splenomegaly, and 1 had biliary mud. Ophthalmological examination was normal in all patients.

Liver biopsy was done for 57 patients (86.4%); 2 patients had granulomatous hepatitis. HAI grading showed mild to minimal inflammation in 51 patients (92.7%) and moderate to marked activity in 4 patients (7.3%). Fibrosis was absent, minimal, or mild in 50 patients (90.9%) and 5 patients had moderate to marked fibrosis.

Response to therapy and predictors of response

At week 8 of therapy, treatment was discontinued for 1 patient due to severe persistent neutropenia even after PEG-IFN dose adjustment. At week 12 of therapy, 31 patients (46.97%) achieved EVR (30 had negative HCV RNA and 1 had >2 log decrease in viral load). Treatment was discontinued for nonresponders. At week 24, 30 patients had negative HCV RNA and completed the treatment for 48 weeks and 1 patient was positive and stopped treatment. At week 48, 29 patients still had negative HCV RNA. At week 72, 1 patient had virologic relapse. Total number of responders who achieved SVR was 28 patients (42.4%) (Fig. 1).

Comparing the group of responders (28 patients), to the nonresponders (37 patients), there was no statistically significant difference regarding sex or age at start of treatment. Although more than 70% of the nonresponders were male, difference in gender did not reach statistical significance. Children who received previous treatment for HCV were comparable in both groups. History of treated malignancies was significantly commoner in nonresponders group ($P = 0.03$).

Pre-enrollment labs showed that responders had significantly higher ANC and lower GGT ($P = 0.009$ and 0.003,

Table 2. Results of Pre-Enrollment Investigations of the Study Group

Laboratory parameter	*Result*
Hemoglobin (gm/dL): Mean ± SD	12.3 ± 1.2
TLC (×10^3/mm^3): Mean ± SD	7.01 ± 2.1
ANC (×10^3/mm^3): Mean ± SD	3.13 ± 1.3
Platelet count (×10^3/mm^3): Mean ± SD	293.7 ± 84.2
Total bilirubin (mg/dL): Median (IQR), range	0.6 (0.4), (0.2–6.9)
Direct bilirubin (mg/dL): Median (IQR), range	0.2 (0.1), (0–3.3)
ALT (U/L): Median (IQR)	52 (47.5)
Number of patients with elevated ALT (%)	36 (54.5)
AST (U/L): Median (IQR)	47.3 (36.8)
Number of patients with elevated AST (%)	33 (50)
AP (U/L): Median (IQR)	207 (125.8)
GGT (U/L): Median (IQR)	26.1 (22.2)
PT (s): Mean ± SD	13.6 ± 0.97
Albumin (gm/dL): Mean ± SD	4.6 ± 0.5
HCV RNA (IU/mL): Median (IQR)	233,809 (1,517,414)

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; IQR, interquartile range; PT, prothrombin time; SD, standard deviation; TLC, total leukocytic count.

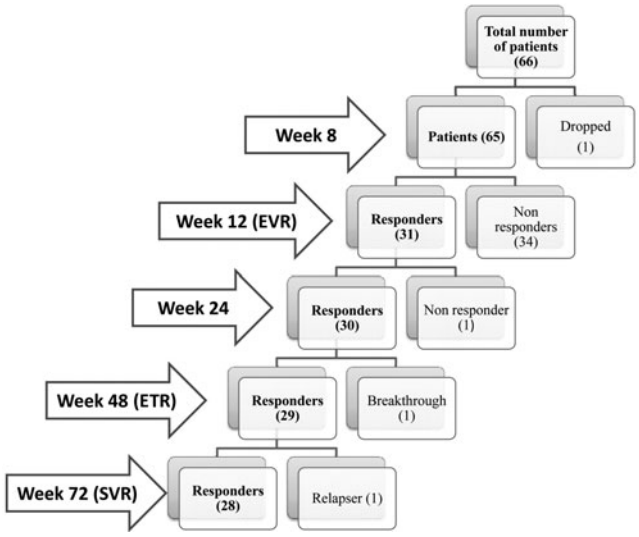

FIG. 1. Response of HCV-infected patients ($n = 66$) to IFN and RBV therapy. ETR, end of treatment response; EVR, early virologic response; HCV, hepatitis C virus; IFN, interferon; RBV, ribavirin; SVR, sustained virological response.

respectively). Viral load was significantly lower in responders ($P = 0.03$). Histopathological examination of liver biopsy showed that moderate and marked degrees of activity and fibrosis were almost all in the nonresponders group; however, the differences did not reach statistical significance (Table 3).

Comparing the pre and post-therapy investigations in the responders group, there was significant reduction in transaminases, AP, hemoglobin, TLC, and ANC (Table 4). All patients with elevated pretreatment AST achieved normalization after therapy, while ALT remained elevated in 7%.

Safety of therapy

Fever was the most frequently reported side effect, occurring in 98.5% of the patients followed by musculoskeletal symptoms (myalgia, arthralgia, and smusculoskeletal pain). The frequency of side effects of therapy are shown in Table 5. Neuropsychiatric manifestations in the form of decreased concentration, depression, and insomnia occurred in 37.9%, 13.6%, and 12.1%, respectively. Constitutional manifestations, especially fever, were frequently observed during the first few weeks of therapy then showed a declining trend through the following weeks. The trend of occurrence of various adverse effects is shown in Fig. 2.

Hematological side effects were documented in a considerable percentage of the patients (Table 4). Neutropenia was observed in 36 patients (54.6%): mild (ANC = 750–1,500/mm^3) in 30 patients and marked (ANC <750/mm^3) in 6 patients (9%). Treatment was discontinued at week 8 in 1 patient. The rest of the patients had dose adjustments for PEG-IFN according to the aforementioned guidelines. Ten patients (15.2%) had anemia with drop of hemoglobin level below 10 gm/dL with dose adjustment of RBV accordingly.

TABLE 3. COMPARISON BETWEEN RESPONDERS AND NONRESPONDERS REGARDING BASIC CHARACTERISTICS AND PRE-ENROLLMENT DATA

	Responders	*Nonresponders*	
Pre-enrollment data	N = *28*	N = *37*	P *value*
Age in years: Mean ± SD	11.6 ± 3.3	10.3 ± 3.6	0.1
Sex: *n* (%)			
Male	16 (57.1)	27 (73)	0.2
Female	12 (42.9)	10 (27)	
Patients who received previous treatment for HCV: *n* (%)	3 (10.7)	7 (18.4)	0.5
Previous treatment for malignancy: *n* (%)	2 (7.1)	11 (28.9)	0.03[a]
Pre-enrollment investigations			
Hemoglobin (gm/dL): Mean ± SD	12.3 ± 0.9	12.3 ± 1.3	0.8
TLC ($\times 10^3$/mm^3): Mean ± SD	7.6 ± 2.2	6.6 ± 2	0.07
ANC ($\times 10^3$/mm^3): Median (IQR)	3.7 (1.6)	2.6 (1.6)	0.009[a]
Platelets ($\times 10^3$/mm^3): Mean ± SD	280.1 ± 65.4	303.4 ± 95.1	0.2
Total bilirubin (mg/dL): Median (IQR)	0.6 (0.4)	0.7 (0.5)	0.6
Direct bilirubin (mg/dL): Median (IQR)	0.2 (0.1)	0.2 (0.1)	0.5
ALT (U/L): Median (IQR)	56.3 (40.5)	45 (69.4)	0.9
AST (U/L): Median (IQR)	47.3 (30.7)	53 (44.2)	0.6
AP (U/L): Median (IQR)	207 (69.2)	198.5 (125)	0.8
GGT (U/L): Median (IQR)	20 (11.9)	31.1 (48)	0.003[a]
Albumin (gm/dL): Mean ± SD	4.6 ± 0.6	4.6 ± 0.5	0.6
PT (s): Mean ± SD	13.7 ± 0.9	13.5 ± 1.05	0.6
HCV RNA (IU/L): Median (IQR)	106,604 (455,850)	350,684 (4,301,535.8)	0.03[a]
Biopsy HAI ($n = 55$): *n* (%)			
Minimal–mild	25 (100)	26 (86.7)	0.1
Moderate–marked	0	4 (13.3)	
Biopsy fibrosis ($n = 55$)			
No/minimal/mild	24 (96)	26 (86.7)	0.4
Moderate/marked	1 (4)	4 (13.3)	

[a]*P* value is significant.
HAI, histological activity index.

Table 4. Comparison Between Pre and Post-Treatment Laboratory Data in the Responders Group ($N=28$)

	Pretreatment	*Post-treatment*	P *value*
Hemoglobin (gm/dL): Mean ± SD	12.3 ± 0.9	11.5 ± 1.3	<0.0001[a]
TLC ($\times 10^3$/mm^3): Mean ± SD	7.6 ± 2.2	5.4 ± 1.4	<0.0001[a]
ANC ($\times 10^3$/mm^3): Mean ± SD	3.52 ± 1.5	2.65 ± 1.3	0.002[a]
Platelets ($\times 10^3$/mm^3): Mean ± SD	280.1 ± 65.4	288.9 ± 68.7	0.4
ALT (U/L): Median (IQR)	57 (45)	30 (13)	<0.0001[a]
Patients with elevated ALT: *n* (%)	18 (64.3)	2 (7.1)	<0.0001[a]
AST (U/L): Median (IQR)	42 (29)	27 (11)	<0.0001[a]
Patients with elevated AST: *n* (%)	13 (46.4)	0	<0.0001[a]
AP (U/L): Mean ± SD	248.1 ± 116.1	146.6 ± 62.4	<0.0001[a]
GGT (U/L): Median (IQR)	20 (12.2)	20 (11)	0.3

[a]*P* value is significant.

Only 1 patient experienced thrombocytopenia with platelet count 64,000/mm^3, which was managed by decreasing the dose of PEG-IFN.

Five patients (7.6%) had elevated level of TSH during the course of therapy. Only 1 patient developed drug-induced hypothyroidism at the 24th week of therapy and was well controlled on L-thyroxine. None of the patients developed retinopathy on follow-up ophthalmological examination. Seventy percent of children, who received the combined therapy for a total of 48 weeks, showed a drop in both weight and height percentiles at the end of the 48 weeks.

Discussion

There are different opinions regarding the need for treatment of children with chronic HCV infection. Treatment may be justified because it allows definitive resolution in these children as later on during adolescence and young adulthood, these patients may become busy with school and work demands, which may result in a lack of compliance with medical regimens and visits. In addition, treatment of young children may be accomplished more easily given motivated caregivers (Mack and others 2012). The clinical course of HCV infection in children and adolescents is usually silent, with minimal histological changes. However, fibrosis is slowly progressive and is related to the duration of infection (Abdel-Hady and others 2011). Hence, successful treatment of patients with chronic infection early in life is recommended to prevent disease progression (Wirth and others 2010). Furthermore, treatment of young children helps in managing psychosocial issues and reduces the effect of treatment on education (Abdel-Hady and others 2014).

Table 5. Frequency of Side Effects Reported in All Patients of the Study Group ($N=66$)

Side effect	N *(%)*
Fever	65 (98.5)
Musculoskeletal symptoms	58 (87.9)
Fatigue	55 (83.3)
Headache	55 (83.3)
Anorexia	53 (80.3)
Vomiting	32 (48.5)
Itching	30 (45.5)
Injection site reaction	30 (45.5)
Dyspepsia	26 (39.4)
Decreased concentration	25 (37.9)
Weight loss	24 (36.4)
Hair loss	23 (34.8)
Chills	19 (28.8)
Skin rash	17 (25.8)
Cough	16 (24.2)
Shortness of breath	15 (22.7)
Nausea	12 (18.2)
Depression	9 (13.6)
Insomnia	8 (12.1)

HCV infection in children is clinically asymptomatic (El-Raziky and others 2007) as histological findings are usually mild and the risk of severe complications is low (Guido and others 2003; Goodman and others 2008; Abdel-Hady and others 2014). In our study, more than 90% of the patients showed minimal or mild degrees in both HAI and fibrosis scores.

Optimal therapy for patients with HCV GT4 infection is changing rapidly and possibility of total cure is near (Esmat and others 2014; Abdel-Razek and Waked 2015). HCV therapy is steadily moving from an immune-based, long-term therapy with significant adverse events and modest efficacy to an all oral, well-tolerated, direct acting antivirals (DAA), short-term, and more efficacious regimen (Cortez and Kottilil 2015). But to date these new drugs have not been approved yet for children. In this study, our treatment regimen was a combination of PEG-IFN-α2b and RBV. The addition of RBV to IFN-α treatment improved SVR (up to 30%–40%) in adults and children (Wirth and others 2010; Schwarz and others 2011).

In children, evaluation of the efficacy and safety of PEG-IFN-α2b and RBV demonstrated higher SVR in GT2 and GT3; and lower SVR in GT1 and GT4 (Wirth and others 2010; Schwarz and others 2011; Abdel-Hady and others 2014). To our knowledge very few studies investigated the effect of combined therapy with PEG-IFN and RBV on GT4 HCV in children (Ghaffar and others 2009; Al Ali and others 2010; El-Naghy and others 2014). One of the strengths of our study is that it was performed on such a large number of exclusively HCV GT4-infected pediatric patients.

In this study, ETR was achieved in 44% and SVR was achieved in 42.4%. The relapse rate was only 1.5%. Relapsers are defined as patients who achieved an ETR but subsequently relapsed and did not achieve an SVR. The relapse rate after treatment with PEG-IFN-α and RBV in adults is 15%–25% (Sarrazin and others 2011).

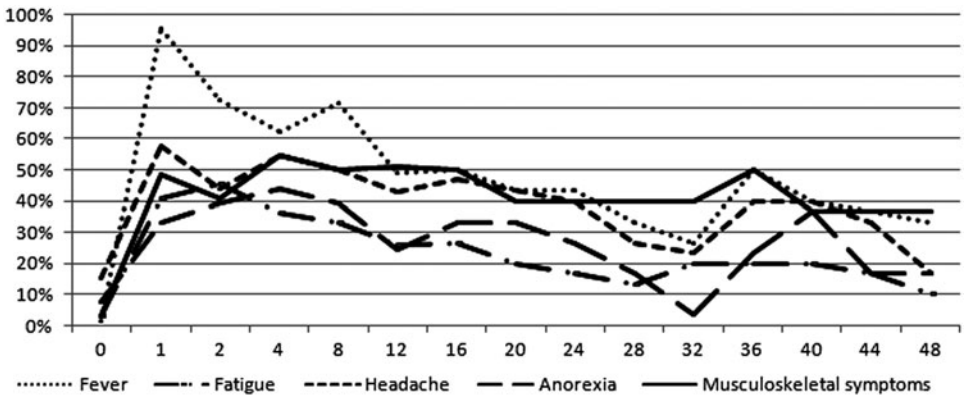

FIG. 2. Trend of adverse side effects throughout the 48 weeks of therapy.

Identification of factors associated with SVR is critical to maximize efficacy and spare patients preventable adverse events and expense. There are several host and viral factors that could influence SVR rates in patients with chronic HCV. To date, HCV GT has been the strongest predictor of treatment response as treatment is more successful in patients with G2 and G3, which determines treatment duration in adults and children (Hadziyannis and others 2004; Baker and others 2007; Jara and others 2008; Ghany and others 2009; Sokal and others 2010; Wirth and others 2010; Schwarz and others 2011). Other factors that could also have higher rates of SVR include younger age (Ferenci and others 2008), female gender (Asselah and others 2010), low pretreatment HCV-RNA levels (Kamal and others 2007; Shiffman and others 2007; Ferenci and others 2008; Lukasiewicz and others 2010), no or minimal liver fibrosis (Kamal and others 2007), rapid virologic response (RVR; Kamal and others 2011; Abdel-Hady and others 2014), IL28B genotype (Rady and others 2015), and adequate adherence to therapy (Lo Re and others 2009). In this study, high pretreatment HCV-RNA level and history of treated malignancies were significantly associated with poor response ($P = 0.03$, $P = 0.03$, respectively).

SVR for the 10 patients who received previous treatment for HCV was 30%. Patients relapsing after treatment with standard IFN-based regimens respond to re-treatment with PEG-IFN-α and RBV in 32%–53% of cases (Sarrazin and others 2011).

Fever, fatigue, and headache were the most frequently reported side effects in this study and were mainly predominant in the first weeks of therapy with decreasing frequency thereafter. The adverse effects of this combination therapy are predominantly side effects of IFN-α and are usually most severe within 24 h of the IFN injection. Many symptoms will wane or resolve after the first few months of therapy (Wirth and others 2005; Foster 2009; Sung and others 2011).

Neuropsychiatric complications occurred in one third of our study group. They can be the most challenging to manage during treatment of HCV infection. IFN-α therapy has been associated with the initiation or worsening of underlying depression, anxiety, and suicidal ideation (Al-Huthail 2006). The onset of neuropsychiatric symptoms may not occur until 3–6 months of therapy (Sung and others 2011).

In this study, neutropenia was considered a common documented adverse event that necessitated treatment discontinuation in only 1 patient. Bone marrow suppression induced by IFN constitutes the next most common toxicity after constitutional symptoms, occurring in approximately one-third of treatment recipients (Druyts and others 2013).

RBV may cause hemolytic anemia that most commonly manifests in the first month of treatment (Abdel-Aziz and others 2011; Sung and others 2011). Ten of our patients (15.2%) manifested mild drop in their hemoglobin level, which was controlled by RBV dose adjustment. Youngest children demonstrated better tolerance to these drugs (Wirth and others 2010).

Thyroid abnormalities are the most common endocrinological adverse effect induced by IFN-α (Sung and others 2011) reaching up to 2%–3% (Wirth and others 2010; Schwarz and others 2011), but permanent endocrinological disorders are uncommon (Serranti and others 2011). One of our patients developed IFN-induced hypothyroidism, which was controlled on L-thyroxin till the end of treatment. Another 4 patients showed elevated level of TSH but with otherwise normal thyroid functions.

A wide variety of ocular complications can occur while receiving IFN-α therapy, such as retinopathy, optic neuritis, and transient monocular blindness (Mehta and others 2010; Narkewicz and others 2010), which was not detected in any of our patients.

Children are susceptible to deficits in growth in weight and height while receiving PEG-IFN-α and RBV. Both PEG-IFN-α and RBV can be associated with anorexia, nausea, and subsequent weight loss (Mack and others 2012). Inhibition of linear growth and weight loss in the treated children was less evident in the group receiving 24-week treatment (Abdel-Hady and others 2014), and the effect was not sustained, which suggests effective catch up (Wirth and others 2010). In this study, both weight and height percentiles showed a decline in 70% of the patients receiving treatment for 48 weeks.

Although in 2014 the World Gastroenterology Organization is still recommending the dual therapy of PEG-IFN-α2b and RBV for patients with HCV in resource-limited regions due to the high cost of new DAAs (Umar and others 2014), these recommendations are now outdated and invalid after the negotiation of the Egyptian government for the relatively low price of sofosbuvir (Abdel-Razek and Waked 2015). Will Egyptian children, infected with HCV GT4, have a similar chance in the nearby future for a safer and more effective therapy? The authors have great hopes in this respect. In view of the aforementioned hopes, we have

recently adopted a new approach in treatment of HCV-infected children. Before administering the currently available therapy, parents would be counseled about the efficacy and side effects of the current therapy and left to choose between: ''yes for current therapy'' or ''wait for newer therapies.'' The former choice is made by parents who worry that infection is associated with ongoing inflammation/fibrosis; they believe that treatment at a younger age with shorter disease duration provides better response and that children suffer less side effects. The latter choice is made by parents if they are aware that most infections in children are asymptomatic; infectivity is less in children; current therapies have side effects and that newer therapies are more effective and will, hopefully, be available soon.

In conclusion, the currently available treatment, PEG-IFN-α2b and RBV, for HCV GT4 in pediatric patients has modest SVR of 42.4% with numerous adverse events necessitating meticulous monitoring to optimize care of the patients. Side effects could be managed with dose modifications and specific treatment when necessary. The future of HCV treatment in children, particularly GT4, requires the development of more effective, better tolerated therapies as has been achieved in adults.

Acknowledgments

This work has been partially funded by the ''Egyptian Liver Care Society.'' The authors would like to thank Mrs. Laila Aly and Mrs. Nariman Mostafa for their secretarial work and patient care throughout the work.

Author Disclosure Statement

No competing financial interests exist.

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Received 28 March 2015/Accepted 12 July 2015