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Original Article

A randomized trial of 24 versus 48 weeks of peginterferon α-2a plus ribavirin in Egyptian patients with hepatitis C virus genotype 4 and rapid viral response

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ABSTRACT

Background and aim: Little data is available regarding the 24-week therapy with pegylated interferon and ribavirin in Egyptian patients with hepatitis C virus (HCV) genotype 4 infection. We aimed to investigate the efficacy of 24-week versus 48-week peginterferon α-2a plus ribavirin therapy in patients with HCV genotype 4 infection with with rapid virological response.

Methods: This trial included 102 patients with HCV genotype 4 infection and low viral load. They were treated with peginterferon α-2a (180 μg/week) plus ribavirin. Patients (87/102) with a rapid virological response were randomized for a total treatment duration of 24 weeks (group A: 43) or 48 weeks (group B:44). Virological responses (EVR: early virological response, EOTR: end of treatment response, and SVR: sustained virological response) were assessed for each group.

Results: In group A, EVR was achieved in 37/43 (84%) patients, while EOTR was achieved in 34/43 (79%) patients and SVR in 30/43 (70%) patients. In group B, on the other hand EVR was achieved in 38/44 (84%) patients, while EOTR was achieved in 35/44 (80%) patients and SVR in 32/44 (73%) patients. No significant difference in SVR rates was observed between the two groups. The rate of adverse events was higher in group B, with lower adherence rates than group A.

Conclusions: In patients with chronic HCV genotype 4 infection with rapid virological response and low viral loads, a 24-week peginterferon α-2a plus ribavirin therapy is as effective as a 48-week therapy with lower rate of adverse events.

KEYWORDS: randomized trial, chronic hepatitis C, peginterferon α-2a, rapid virological response, genotype 4, pretreatment viral load

Introduction

HCV genotype 4 (HCV-4) infection is common in the Middle East and in Africa, where it is responsible for more than 80% of HCV infections. It has recently spread to several European countries. HCV-4 is considered a major cause of chronic liver disease and cirrhosis, which leads to liver failure and is the root cause of hepatocellular carcinoma.[1,2]

Interferon (IFN) based treatment of HCV infected patients can achieve viral clearance and thereby improves their histology and prognosis.[3,4] The primary aim of antiviral therapy in patients with chronic hepatitis C is a sustained virological response (SVR), defined as undetectable serum HCV RNA by a sensitive molecular assay 24 weeks after end of treatment. A combination therapy of peginterferon and ribavirin is currently recognized as the standard treatment for chronic hepatitis C, resulting in a 40–50% SVR rate in patients infected with HCV genotype 1 and around 80% in those infected with HCV genotype 2 or 3.[5–7]

Response-guided therapy is a paradigm for treating chronic hepatitis C infection in which treatment decisions are based on how rapidly hepatitis C virus responds to treatment. With response-guided therapy, patients who rapidly clear the virus from their bloodstream are eligible to receive a shorter duration of therapy, while slow responders receive standard or extended durations of therapy. Use of response-guided therapy is already well reported in easier-to-treat genotypes of HCV, specifically genotypes 2 and 3; and recently for genotype-1 HCV infection with direct-acting antiviral agents.[8]

The aim of this study was to compare the efficacy and safety of 24 versus 48 weeks of peginterferon α-2a plus ribavirin in Egyptian patients chronically infected with hepatitis C virus genotype 4 with rapid viral response to combination therapy.

Methods

Patient selection

Adult patients with chronic HCV infection who had the following characteristics were enrolled for the study: (1) a positive test for anti-HCV antibody and HCV PCR, (2) HCV genotype 4 and an HCV RNA level less than 600,000 IU/ml, (3) minimum baseline neutrophil and platelet counts of 1500/μl and 100,000/μl, respectively, and a baseline hemoglobin level of at least 12g/dl. Patients with following exclusion criteria were not included in the study: other viral infections such as hepatitis B, human immunodeficiency virus; any other cause of liver disease such as autoimmune hepatitis, primary biliary cirrhosis, drug-induced liver disease, and excessive daily intake of alcohol; relevant confounding disorders including decompensated liver disease, hepatocellular carcinoma, and other malignant neoplastic disease; concomitant use of immunosuppressive drugs; neurological or psychiatric diseases; and allergy to peginterferon α-2a or other interferons and biological preparations including vaccines.

Study design

This study was a multicenter, open-label, randomized trial. We compared the efficacy and safety of 24 vs. 48 weeks of treatment with peginterferon α-2a plus ribavirin in patients with chronic HCV genotype 4 infection with low viral loads, who showed rapid virological response to peginterferon ribavirin therapy. All patients were treatment-naïve. Eligible patients were treated with peginterferon α-2a at a dose of 180 μg once per week subcutaneously plus ribavirin at a dose of 1000-1200 mg/day according to body weight. After achieving rapid virological response (RVR), patients were randomized either for total treatment duration of 24 weeks (group A) or for 48 weeks (group B). Patients were assigned upon a report of RVR to group A or B with a computer-based random allocation system by a researcher who was independent of the study, and the allocation system was not accessible to any of the investigators who enrolled patients for the study. The system was neither stratified nor blocked. After the end of treatment, all patients were followed for an additional 24-week period.

The non-inferiority margin was set at 10% between both groups. A sample size calculation based on typical values for significance level (5%) and power (80%) yielded an estimated sample size of 40 patients in each group. To enroll these 80 patients we took into consideration the expected RVR, and we included 102 patients.

The study was approved by the ethics committees of our centers and all study procedures were carried out according to the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Virological and histological evaluation

Serum HCV RNA was detected by qualitative reverse-transcription polymerase chain reaction (RT-PCR, Amplicor HCV, Roche Diagnostics Tokyo, Japan); with a lower limit of detection of 50 IU/ml. The serum HCV load was determined by quantitative RT-PCR (Amplicor HCV Monitor Test, Version 2.0, Roche Diagnostics, Japan); which had a lower limit of detection of 500 IU/ml. HCV RNA genotype was determined by RT-PCR using genotype-specific primers.[9] All patients underwent liver biopsy before therapy. Histopathology results were classified

by local pathologists according to the METAVIR criteria reported previously.[10,11]

Follow-up of patients

Patients were evaluated as outpatients for treatment safety, tolerance and efficacy by each attending physician every week during treatment and every 4 weeks after the end of treatment for the rest of the study period. The group receiving treatment for 24 weeks were followed for a total of 48 weeks while the group receiving treatment for 48 weeks were followed for a total of 72 weeks.

Assessment of efficacy

The RVR was determined by qualitative PCR. During treatment the early viral response was tested by quantitative PCR. The EOTR and SVR on the other hand were assessed by qualitative PCR assay. EOTR was defined as undetectable serum HCV RNA level at the end of treatment. SVR was defined as undetectable serum HCV RNA level by the end of treatment and throughout the follow-up period at least 6 months after the end of treatment.

Safety analysis

Patients were assessed for safety and tolerance by the attending physician, by monitoring adverse events and laboratory value abnormalities. The study protocol permitted dose modification for patients who had clinically significant adverse events or important abnormalities in laboratory values. Adverse events were handled according to the instructions provided by the manufacturer for peginterferon α-2a or ribavirin, and appropriate therapy adjustments were applied. In general, dose reductions and discontinuation of therapy, if any, were made following the recommendations of the manufacturer. The dose was also reduced or the drug was discontinued on the basis of the results of hematological, neuropsychiatric and cutaneous or other adverse effects that were considered related to the medication. The dose of any medication could be restored to their original levels upon resolution of the event or abnormality.

Adherence to therapy was assessed as described previously,[12] namely, by calculating the actual doses of IFN received as a percentage of the expected dose. Thus, patients who received 80% or more of their total IFN doses for 80% or more of the expected duration of therapy were considered to be 80% adherent.

End points

Analyses included data from all patients who underwent randomization. The primary end point was either an SVR, defined as undetectable HCV RNA levels 24 weeks after the completion of therapy or breakthrough defined as reappearance of viremia during treatment after initial response or relapse, defined as an undetectable HCV RNA level at the end of the treatment phase, with a detectable HCV RNA level during the follow-up period.

Statistical analysis

The primary objective of the study was to establish the difference in SVR rates between treatment groups A and B. Results were expressed as mean ± standard deviation (SD), median (interquartile range) or numbers (%). Differences between treatment groups were compared statistically by analysis of variance, Chi square test, Fisher's exact test, and Kruskal–Wallis test, where appropriate. SPSS statistical package version 11.0 was used for data analysis. A p value equal to or less than 0.05 was considered significant.

Results

Of the 186 patients screened for this study, between January 2007 and December 2009, a total of 102 patients were treated for chronic HCV infections. Out of 102 treated patients, 87 showed RVR and underwent randomization, to be assigned into group A (n = 43) treated for 24 weeks and group B (n = 44) treated for 48 weeks (**Figure 1**). There were no significant differences in baseline parameters between the two groups (**Table 1**).

Virological response

An overall intention-to-treat virological response at the end of treatment was achieved in 69 of 87 (79%) patients and SVR in 62 of 87 (71%) patients. In group A, EVR was achieved in 37/43 (84%) patients, while EOTR was achieved in 34/43 (79%) patients and SVR in 30/43 (70%) patients. In group B, EVR was achieved in 38/44 (84%) patients, while EOTR was achieved in 35/44 (80%) patients and SVR in 32/44 (73%) patients (**Figures 2 and 3**). No significant difference between the SVR rates was

observed between the two groups.

Safety and adherence to therapy

Six patients (7%) discontinued therapy (2 in group A and 4 in group B): 2 patients because of severe depression; another 2 because of anemia and/or severe neutropenia; and 2 other patients refused to continue treatment. The frequency of discontinuation of therapy was lower but not significant in group A (**Table 2**).

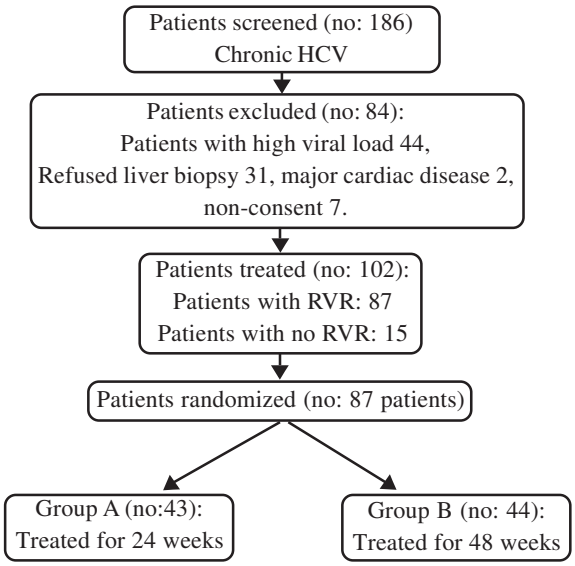

Figure 1: Trial profile: HCV : hepatitis C virus, RVR: rapid viral response. Low viral load < 600.000 IU/ml

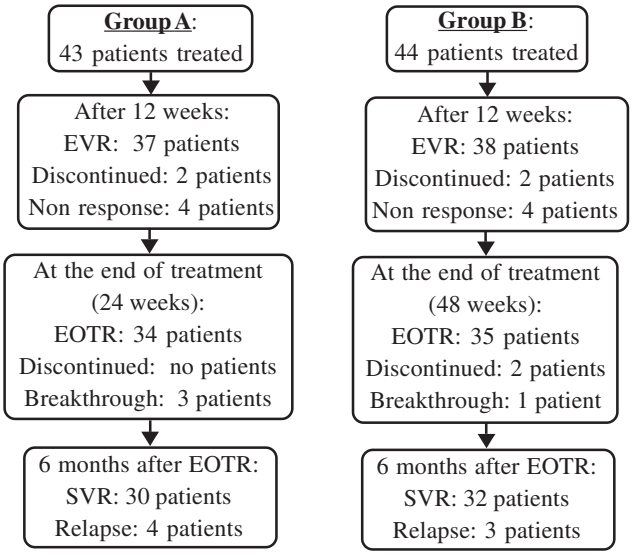

Figure 2: Protocol analysis for viral response to therapy. EVR (early virological response), EOTR (end of treatment response), SVR (sustained viral response). Breakthrough: reappearance of viremia after EVV. Relapse: reappearance of viremia 6 months after treatment.

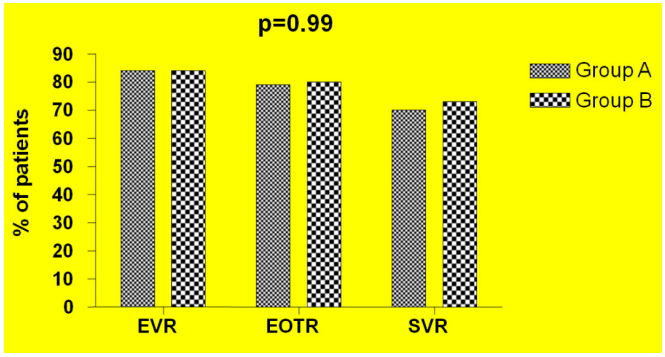

Figure 3: Virological responses in both groups on combination therapy: EVR (early virological response), EOTR (end of treatment response), SVR (sustained viral response). Group A: 43 patients treated for 24 weeks and group B: 44 patients treated for 48 weeks

Table 1: Baseline demographic and disease characteristics of the study patients

	Group A	Group B
Age (in years)	42 ± 4.9	41.11 ± 8.3
Sex (number and % of males)	33/43 (77%)	32/44 (73%)
BMI	30.6 ± 4.7	29.7.9 ± 3.9
ALT level (median (range)	68 (48-148)	66 (45-166)
AST level (median (range)	65 (42-123)	67 (43-122)
HCV RNA	135490 (11760-592000)	144640 (5500-570000)
Fibrosis: METAVIR fibrosis score	5/22/4/11	6/27/3/8
F1/F2/F3/F4: number (%)	12%/52%/10%/26%	14%/61%/7%/18%
Steatosis: patients with fatty liverNumber (%)	20/43 (47%)	21/44 (48%)
Hemoglobin	13.2 ± 1.0	13.3 ± 1.1
Neutrophil count	2332 ± 1108	2455 ± 1220
Platelet count	168 ± 42	173 ± 65

ALT alanine aminotransferase, AST: aspartate transaminase
Data are : mean ± SD or median (interquartile range),

Table 2: Adverse events and discontinuation of therapy according to treatment group

	Group A (n=43)	Group B (n=44)	p-value
Adverse events			
Fatigue	16	28	0.019
Depression	2	3	1.000
Arthralgia	12	16	0.492
Arrhythmia	0	1	1.000
Pyrexia	5	9	0.382
Headache	8	14	0.468
Hypothyroidism	2	6	0.265
Laboratory abnormality			
Anemia	14	28	0.005
Neutropenia	10	18	0.108
Elevated aminotransferase	8	11	0.605
Discontinuation of therapy*:	2	4	0.676
- patient refusal	1	1	
- adverse events	1	3	

** Discontinuation of therapy due to causes other than non response to therapy. In group A: a withdrawl of consent, severe depression. In group B: withdrawl of consent, neutropenia, severe anemia, depression.*

Fatigue and anemia were more frequent in the 48-week treatment group (group B) than in the 24-week treatment group (group A) (64% vs. 37%, p = 0.019 and 64% vs. 33%, p = 0.005, respectively). Adherence to scheduled therapy (median and interquartile range) was 100% (68–100%) in group A versus 74% (52–100%) in group B (p = 0.01). The rate of adherence in group A was higher than in groups B (p = 0.003). Thus, adherence to therapy in the longer treatment course (48 weeks) was lower than in the shorter treatment course (24 weeks).

Costs

Based on the current prices in Egypt for one patient, total spending on medication for 48 weeks of peginterferon α-2a plus ribavirin is $10,000 and that for 24 weeks treatment is $5,000. So according to the results of our study, considering the rate of SVR, a budget of total cost of treating 100 patients with rapid virological response and low viral load will be around $ 500,000 to cure 70 patients and accordingly $ 715,000 to cure 100 patients when treating them for 24 weeks. If we consider treatment for 48 weeks, the total cost will be around $ 1000,000 to cure 73 patients and we'll need a budget of $ 1,370,000 to cure 100 patients. Thus curative treatment of 100 patients based on a 24-week course may save $ 655,000

Discussion

The key finding of this study is that in patients infected with HCV genotype 4 and low viral load who achieve RVR, a 24-week treatment with peginterferon α-2a plus ribavirin may be sufficient in terms of efficacy. A 24-weeks therapy has higher adherence rates, lower rates of adverse events and accrues lower cost. Thus, by reducing the treatment period, these patients can avoid unnecessary treatment without compromising their chances for an SVR.

Response-guided therapy is an approach for treating chronic hepatitis C infection in which treatment decisions are based on how rapidly hepatitis C virus responds to treatment. Use of response-guided therapy is already well reported in easier-to-treat genotypes of HCV, specifically genotypes 2 and 3; and recently has been employed for genotype 1 HCV infections as well. This approach would allow many patients to be treated with just 24 weeks of therapy instead of the standard 48 weeks of treatment.[8,13]

In this study, we recruited patients with genotype 4 infection which is predominant in Egypt and well known for its difficult treatment. We included patients with low viral loads and RVR, as these two factors are the most important predictors of response in patients with chronic HCV.[13,14] The SVR in our study was comparable between the group receiving 24 weeks of therapy (70%) and the group receiving 48 weeks of therapy (73%), with nearly equal efficacy of treatment in both groups.

In various studies from European and Middle Eastern countries, SVR rates ranging from 43 to 70% have been reported.[15-18] These results were lower (42–46%) in genotype 1 infected patients than those (76–82%) reported in patients with chronic hepatitis C genotypes 2 and 3.

Forty-eight-week regimens were recommended for patients infected with HCV-1 and 4. This recommendation is based on the results of large randomized, international, phase

III trials of peginterferon alfa-2 combined with ribavirin.[19-22] Unfortunately these studies included very few patients with HCV-4. There are two trials that were conducted in patients with HCV-4, reporting viral response at week 4. These studies were conducted in Europe and Egypt. The SVR in these studies was around 86%. The investigators concluded that patients with HCV-4 who achieve an RVR are potential candidates for abbreviated 24-week treatment regimens, provided that no other predictors of poor response are present.[23,24] The relative lower SVR rate in our study may be explained by inclusion of patients with high fibrosis score. Similar to our observations, all other studies have demonstrated lower cost, higher adherence rates and lower incidence of adverse events in the abbreviated 24-week regime. Unfortunately, in contrast to patients with HCV-1 the concept of response-guided therapy has not been validated in patients with HCV-4. In the absence of any consensus data for HCV-4 patients, we suggest that similar response-guided approach as employed for HCV-1 patients, may be considered for HCV-4 patients as well.

In a recent published review, an international panel of experts has proposed an algorithm for treating patients with chronic HCV-4 based on the kinetics of viral response (response-guided therapy). In this algorithm, patients with genotype 4 who achieve rapid viral response may be treated for only 24 weeks in absence of any predictors of poor response, which include high basal viral loads (≥800,000), advanced degree of fibrosis (≥F3,4), and high degree of basal insulin resistance (HOMA-IR ≥2).[25] The lower incidence of side effects with the 24-week regimen lends the patient the additional benefits of better quality of life, better compliance and adherence to treatment.

In conclusion, our findings suggests that patients infected

with HCV genotype 4 with low baseline viral loads, who can achieve RVR, can be satisfactorily treated on a 24-week regimen of peginterferon α-2a plus ribavirin, without compromising the SVR. Additional trials on larger cohorts are recommended to optimize the treatment schedule in such patients.

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