DIFFERENT, PEGYLATED INTERFERON- RIBAVIRIN THERAPY IN NON-RESPONDERS WITH CHRONIC HEPATITIS C VIRUS INFECTION

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ABSTRACT

Background: PEGylated interferon and ribavirin therapy is the current standard of care for patients with chronic Hepatitis C virus. It is unknown whether retreatment may be beneficial in non-responders.

Methods: Patients who failed to respond to either PEG-Intron or Pegasys with ribavirin were switched to a different PEGylated interferon with ribavirin.

Patients were assessed for virologic response by a decrease in viral load levels using a polymerase chain reaction assay. Only patients who had a negative viral load at week 24 were allowed to continue treatment for 48 weeks. Patients with a negative polymerase chain reaction assay after 6 months of treatment were considered as responders to the retreatment regimen.

Results: A total of 16 patients were retreated. The combination of Pegasys and ribavirin was administered to 3 patients, and 13 patients received PEG-Intron with ribavirin. Patients had either genotype 1 or 4. Only 4 patients responded to retreatment with PEG-Intron (25%).

The responders were female, had a low viral load and had an early significant viral load reduction. Three patients had genotype 4, and one had genotype 1.

Conclusion: Retreatment with different PEGylated interferon in patients who failed previous treatment may have a role in the selected patients infected with chronic Hepatitis C virus.

Keywords: Hepatitis C, PEGylated interferon, Ribavirin, Non-responders.
Hepatitis C
Currently, more than 170 million people are infected with Hepatitis C virus (HCV) worldwide, with more than 80% developing chronic liver disease[1-3]. Since the approval of alpha interferon (IFN) for the treatment of patients who are chronically infected with HCV, several developments have been made to improve patient response. Despite the current recommendation of using a combination of a PEGylated interferon (PEG IFN) and ribavirin (RBV), a considerable number of patients fail to clear the virus, with a 50% cure rate across genotypes[4-8]. Patients who fail to respond are difficult to treat, and several modifications of treatment have recently been considered to improve patient response, including the addition of a protease inhibitor to combination therapy in patients with genotype 1[9].

The primary objective of this study was to assess whether retreatment with different PEG IFNs has a role in patients who previously failed to respond. The most commonly used PEG IFNs are PEGylated interferon alpha 2b, manufactured by Merck (PEG Intron), and PEGylated alpha 2a, manufactured by Roche (Pegasys). The two PEGylated interferons differ according to the polyethylene glycol molecule (PEG) attached to interferon; PEG is large (40 KD) and branched in Pegasys, and the un-branched and small (12 KD) in PEG Intron[10,11].

In addition, Pegasys has a relatively constant absorption after injection, and is distributed mainly in the blood and organs. PEG-Intron has a rapid absorption and a wide distribution in the body[12].

METHODS

Study Patients
Patients chronically infected with HCV who were previously treated with a PEG IFN and RBV and failed to respond were retreated with different PEG IFN together with RBV.

Patients involved in the study were outpatients treated from 2006-2010, and were considered eligible if they were willing to be treated again within 2 years after previous treatment failure (6 months minimum). The exclusion criteria included co-infection with Hepatitis B or other causes of chronic liver disease, decompensated liver disease, and the presence of esophageal or gastric varices, severe psychiatric disorders and previous intolerance to PEG IFN.

Study Design
Patients who failed to respond to Pegasys and RBV were retreated once weekly with PEG-Intron (1.5 μg/kg body weight), subcutaneously (S/C) and RBV. Patients who failed treatment with PEG Intron/RBV received once-weekly treatment with Pegasys (180 μg) S/C and RBV. The ribavirin dose was scheduled as 800 mg daily for genotypes 2 and 3 (although none of the patients in the study were genotype 2 or 3), 1000 mg daily for patients with genotype 1 or 4 weighing less than 75 kg, and 1200 mg daily for patients with genotype 1 or 4 weighing more than 75 kg in divided doses.

Patients underwent baseline complete blood count (CBC), liver function (LFT), prothrombin time (PT), Hepatitis B surface antigen (HBsAg), antinuclear antibody (ANA), quantitative Hepatitis C virus ribonucleic acid polymerase chain reaction (HCV RNA PCR, using a TaqMan 2.0 assay with a lower limit of detection of 12 IU per milliliter) and HCV genotyping (determined with the HCV 5 noncoding region) tests. Abdominal ultrasonography and gastroscopy were also performed to rule out the presence of varices.

Data regarding previous treatment were collected, including drugs used, dose and duration, previous response status, compliance, significant side effects, and the time and reason for treatment discontinuation.

The response was assessed by more than a 2-log decrease in HCV RNA levels at 4 weeks (rapid virologic response, RVR), an undetectable HCV RNA level at 12 weeks (early virologic response, EVR) and an undetectable HCV RNA level at 48 weeks (end therapy response, ETR). HCV RNA PCR (quantitative) was repeated after 6 months after treatment, and if the results were negative, the patient was labeled as having a sustained virologic response (SVR). The stopping rule was applied to patients who failed to achieve undetectable HCV RNA levels at week 24.

Statistical Analysis
The Statistical Package for the Social Sciences (SPSS 16) was used, and descriptive statistics were obtained. The Mann-Whitney test was used to compare HCV PCR results between the different variables. A regression analysis was used to define the relationship between retreatment SVR and different variables.

Patient Characteristics
A total of 19 patients were evaluated for enrollment in the study. Three patients were subsequently excluded due to low platelet counts in 2 patients (97 and 84 x103/microliter) and the presence of esophageal varices (grade II-III) in all 3 patients.

The final analysis included 16 patients, 13 of whom were Saudi patients (81.2%). There were 8 males and 8 females. The mean age was 43.44 ± 4.42 years (29-57 years). The mean weight was 75.62 ± 7.44 kg (55-97 kg). Ten patients had genotype 4 (62.5%), and the remaining 6 patients (37.5%) had genotype 1 (Table1).

Previous Treatment Outcomes
All of the patients insisted that they were compliant to the previous treatment regimens, which were 180 μg Pegasys and 100 μg PEG Intron.

Eleven patients were previously treated for 24 weeks or less. The main reason for treatment discontinuation at 24 weeks or earlier was failure to achieve a virologic response (undetectable or less than a 2-log decrease in viral load as indicated by PCR). However, in one patient who developed hypothyroidism, the treatment was stopped at 8 weeks at the patient’s request. One patient received treatment for 36 weeks after testing negative for HCV by PCR and had
a subsequent relapse after 3 months without treatment. Out of the 4 patients who completed 48 weeks of therapy, only 2 patients achieved an ETR, but none achieved an SVR (Table 2).

Retreatment Patient Characteristics
Thirteen of the study subjects had a failure of previous Pegasys treatment (Group 1), and 3 patients had failure of previous PEG-Intron treatment (Group 2). The mean baseline HCV PCR resulted before retreatments were $6.75 \times 10^5 \pm 232 \times 10^3$ international units per milliliter (IU/ml). Five patients (31.2%) had a high viral load (HCV RNA PCR level > 8000 $10^3$ IU/ml). Patients who were retreated with Pegasys received 1200 mg RBV (weight greater than 75 kg). Of the 13 patients who were retreated with PEG Intron, only 6 continued on 1200 mg RBV; 3 patients had RBV reduced to 800 mg, and 4 patients had a dose reduction to 600 mg because of anemia. Four patients from Group 1 (25% of all retreated patients) achieved an RVR: 3 had completed viral clearance at 4 weeks, and the 4th had more than a 2-log decrease at 12 weeks during previous treatment and an RVR with the retreatment regimen. A similar study showed that Retreating with Peg-Intron and a weight-based dose resulted in an RVR rate of only 2%.

Table 1. Patients’ characteristics.

| Sex          | Male N = 8 | Female N = 8 |
|--------------|------------|--------------|
| Age (years)  | 45.12 ± 7.51 | 41.75 ± 6.47 |
| Weight (kg)  | 73.88 ± 13.00 | 77.88 ± 10.75 |
| Saudi (81.25%) | 7 | 6 |
| Non-Saudi (18.75%) | 1 | 2 |
| Genotype 1 (37.5%) | 3 | 3 |
| Genotype 4 (62.5%) | 5 | 5 |

Table 2. Previous treatment outcome.

| Duration | Patients (16) | ETR |
|----------|--------------|-----|
| 24 weeks or less | 11 (68.75%) | 0 |
| 36 weeks | 1 (6.25%) | 1 |
| 48 weeks | 4 (25%) | 2 |

Table 3. Retreatment outcome.

| Duration | Group 1 (13 patients) | Group 2 (3 patients) |
|----------|------------------------|----------------------|
| RVR      | 4                      | 0                    |
| SVR      | 4                      | 0                    |

Table 4. Effect of age, weight and PCR results on retreatment SVR.

| Sex          | Standardized Coefficients | Significance |
|--------------|----------------------------|--------------|
| Age          | -0.743                    | .004         |
| Weight       | 0.070                     | .744         |
| PCR          | -0.714                    | .004         |

Retreatment Duration
All of the patients were compliant and adherent to treatment. One patient who had a ribavirin dose reduction to 600 mg (hemoglobin 9.1 g/dl) stopped treatment at 3 months on his request (Group 1). The four patients who responded continued treatment for one year (48 weeks). Treatment was stopped for all of the other patients with positive PCR results at 6 months as per protocol.

DISCUSSION
Patients who fail to have a virologic response with PEG IFN and RBV therapy should not be retreated with the same regimen if they were compliant with their therapy for it will result in the same non-response.

The data from this study show that patients who failed to respond to previous combination PEG IFN/RBV therapy may respond to retreatment with a different PEG IFN. Although this result was found only with PEG-Intron in patients previously treated with Pegasys, this effect could be underestimated as there were only 3 patients in Group 2. Patients who showed a response were female, had a low viral load (less than 800,000 IU/ml), and had more than a 2-log decrease at 12 weeks during previous treatment and an RVR with the retreatment regimen. A similar study showed that retreatment with Peg-Intron and a weight-based RBV dose resulted in an SVR rate of only 17%. Relapse after previous PEG IFN-based therapy was associated with a strong
probability of treatment success, whereas the retreatment of patients with a previous nonresponse was not [13].

Several studies have been conducted on patients infected with HCV who failed treatment. This group included maintenance therapy with PEG IFN or RBV to ameliorate disease activity rather than viral eradication, and the treatment was shown to be ineffective. The use of consensus interferon plus ribavirin was shown to have a modest response (22%). Extending treatment for 72 weeks or a higher dose of PEG IFN did not demonstrate sufficient benefit to support such strategies [14-17].

Recently, 2 protease inhibitors have been approved for treating patients infected with HCV genotype 1 (boceprevir and telaprevir). The addition of HCV protease inhibitors to standard therapy with PEG IFN/RBV significantly increases the rates of sustained virologic responses in patients infected with HCV genotype 1 in both, those who were previously untreated and those in whom prior treatment had failed [18-21].

The majority of patients infected with HCV in Saudi Arabia are infected with genotype 4, which makes the option of using HCV protease inhibitors in patients who failed previous treatment not feasible [22,23].

However, until now, there has been no standardized approach to the management of non-responders infected with non-genotype 1 HCV. PEG IFN in combination with RBV may be considered as a treatment option in patients who failed prior IFN therapy. Several prospective studies have found that non-responders to prior courses of standard IFN monotherapy and relapses following standard IFN, with or without RBV, may derive the most benefit from retreatment with PEG IFN and RBV. Prior non-responders to standard IFN monotherapy achieve SVR rates ranging from 21% to 28% with PEG IFN and RBV treatment. Whereas, relapers combined standard IFN and RBV have been reported to achieve an SVR in 38% to 58% of cases with PEG IFN and RBV. In contrast, null responders to combination therapy with IFN and RBV tend to demonstrate relatively poor responses to retreatment with PEG IFN and RBV, with an SVR ranging from 8% to 15% [24,25]. Management remains a challenge in this group of patients who fail to respond to PEG IFN/RBV treatment; optimizing the modifiable predictors of non-response, including adherence and compliance to therapy, can help to increase the virologic response [26].

Currently, retreatment with different PEG IFNs should be considered in selected patients. Including those patients with a low viral load and those who had more than 2-log decrease in viral load or relapers after previous PEG IFN/RBV therapy, rather than null responders, until more effective drugs become available. The early stoppage rule at 12 weeks can be applied if patients do not achieve an ETR, which will reduce further costs and side effects.
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