Effect of pegylated interferon on non-responders and relapsers with interferon

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فاعلية العلاج بعقار الانترفيرون المحسـن لدى مرضى الفيروس الكبدى نوع ج والغير مسـتجيبين للانترفيرون التقليدى

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المسـتخلص: الهدف: التحقق من فاعلية الانترفيرون المحسـن لدى مرضى مصابين بفيروس الالتهاب الكبدى نوع ج والغير مسـتجيبين للانترفيرون التقليدى . **الطريقة:** تم علاج ٢٠ مريضا لم يسـتجيبوا سـابقا لعلاج الانترفيرون بدواء الانترفيرون المحسـن مع الريبافيرين لمدة سـنة واحدة.**النتائج:** اسـتجاب ٧ مرضى في نهاية العلاج واسـتمرت اسـتجابة مريضين فقط بعد سـتة اشـهر من ايقافة وتبين انهما كانا من المسـتجيبين مع نهاية العلاج بالانترفيرون سـابقا ولكن لم تسـتمر الاسـتجابة بعد ايقافه.**الخلاصة:** ان علاج الانترفيرون المحسـن ربما يكون ناجعا للمرضى الذين لم تسـتمر اسـتجابتهم مع علاج الانترفيرون التقليدى.

ABSTRACT. *Objectives*: To assess whether a combination of pegylated interferon (interferon conjugated with polyethylene glycol) and ribavirin can improve the response rate in patients with chronic hepatitis C who either did not respond to (Non-responders), or had relapsed after responding to (Relapsers) standard interferon and ribavirin combination therapy. *Patients and methods*: In this prospective study, 20 chronic hepatitis C patients (comprising 16 Non-responders and 4 Relapsers to previous treatment with alpha interferon and ribavirin), were treated with pegylated interferon-2b weekly and ribavirin daily for one year. Eleven patients had genotype 4, eight were of genotype 1 and one patient had genotype 3. Response to treatment was determined based on normalisation of liver enzymes and negative viral load (assessed using qualitative HCV RNA PCR) at end of treatment (ETR) and 6 months off treatment (SVR). *Results*: Seven patients (35%) achieved normalisation of liver enzymes and negative viral load at the end of treatment. However, only 2 patients (10%) managed to retain these levels after six months off treatment. The latter two patients had been previous Relapsers. *Conclusion*: Combination of pegylated interferon and ribavirin may be beneficial in previous relapsers with standard interferon-ribavirin combination therapy, but is unlikely to achieve sustained virological response in non-responders.

Key words: pegylated interferon, ribavirin, hepatitis C virus, non-responders, relapsers

TREATMENT OF HEPATITIS C VIRUS (HCV) infections has been a subject of different studies. Alpha-interferon was the first drug approved for treatment of HCV. Initially interferon monotherapy for 6 months was a common practice but it was associated with high relapse rates.[1] Extended treatment with interferon for one year was found to decrease the relapse rate and increase sustained response.[2,3] Subsequently ribavirin was approved for treating HCV in combination with interferon. One year-long interferon-ribavirin combination therapy resulted in higher response.[4,5] Despite such improvement, there are many patients who do not respond to treatment or relapse off treatment. Recently, pegylated interferon has been approved for treatment of patients with chronic HCV. Attachment of polyethylene glycol molecule to interferon (*pegylation*) has the advantage of prolonged action as compared to regular interferon. Several studies have shown pegylated interferon's superiority in improving response rate in naïve patients, alone or in combination with ribavirin.[6-9] This additional effect is yet to be proven on previous non-responders or those who relapsed after combination therapy with ribavirin and interferon.

PATIENTS AND METHODS:

Patients who had been treated earlier with combination therapy (interferon and ribavirin) for one year and did not respond or had relapsed off treatment, were considered for this study. *Non-responders* were defined as those patients who, during treatment, had increased liver enzymes (AST/ALT) and persistent detectable viral load, measured using qualitative HCV RNA PCR (Roche

Diagnostics). *Relapsers* were those patients who had normal liver enzymes and undetectable viral load (HCV RNA PCR-qualitative) at end of treatment that was not persistent 6 months after stopping combination therapy. All patients were at least 6 months and not more than 2 years off-treatment.

End of Treatment Response (ETR) was defined as normalisation of liver enzymes and negative HCV RNA PCR (qualitative) at end of treatment. *Sustained Virologic Response* (SVR) was defined as persistent normalisation of liver enzymes and negative HCV RNA PCR (qualitative) 6 months off treatment. SPSS statistical package was used for analysis. Descriptive statistics were done. P-value was set at <0.05 for statistical significance.

PATIENT CHARACTERISTICS

Twenty patients, comprising 16 Non-responders and 4 Relapsers (to a previous combination treatment) were included in the study. The patients were followed for the period from March 2000 to November 2001 at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. Before treatment, complete blood count (CBC), liver function test (LFT), prothrombin time (PT), thyroid function test (TFT/T4, TSH), quantitative HCV RNA PCR (Roche Diagnostics), gastroscopy and abdominal ultrasound were conducted. Quantitative HCV RNA PCR results were grouped into low (<106 copies/ml), moderate (106–107 copies/ml) and high (>107 copies/ml). Previous liver biopsy results before treatment with combination therapy were considered while assessing patient response to pegylated interferon. Histological severity using grading for necroinflammatory activity and staging for degree of fibrosis was reported as mild hepatitis (grade 2, stage 1), moderate hepatitis (grade>2, stage 2), severe hepatitis (grade>2, stage 3) and liver cirrhosis (stage 4). Patients included in the study were started on pegylated interferon-2b (Schering Plough USA) 100 mcg subcutaneously weekly, together with ribavirin (400 mg) twice daily for one year. CBC and LFT were repeated weekly for the first month and then monthly until the end of treatment. TFT and qualitative HCV RNA PCR were repeated after 6 months, end of treatment (12 months) and 6 months off treatment together with LFT. The patients had given their written consent. Female patients were instructed to practise contraception during childbearing period.

Fourteen patients (70%) were male and 6 (30%) were female. Their mean age was 41 years (29–61 years), and average weight, 74.4 kg (53–94 kg). None of the patients had esophageal varices, and their abdominal ultra-sound did not show evidence of ascites, splenomegaly or focal liver lesions. Viral load was low in three patients (15%), moderate in 16 patients (80%), and high in one patient (5%). Eleven patients (55%) were of genotype 4, five patients (25%) had genotype 1a, three patients (15%) had genotype 1b, and one patient (5%) had genotype 3 (consistent with the most prevalent genotypes among this community where genotypes 1 and 4 account for > 86.4%). Two patients (10%) had mild hepatitis, 8 patients (40%) had moderate hepatitis, 6 patients (30%) had severe hepatitis and 4 patients (20%) had liver cirrhosis.

RESULTS

Seven patients (35%) achieved ETR with pegylated interferon and ribavirin, and 3 of them had low viral load and 4 had moderate viral load; 2 patients had mild hepatitis and 4 had moderate hepatitis. Four patients had already achieved ETR with previous treatment with regular interferon combination therapy, but were Relapsers, and 3 patients were Non-responders. Two patients (10%) had SVR (genotype 1a,3) while another patient, of genotype 4, had persistent normal AST level with positive HCV RNA PCR 6 months off treatment (*Sustained Biochemical Response* – SBR). All patients who had SVR or SBR were Relapsers [Table 1]. Patients who achieved ETR with the current treatment had already negative HCV RNA PCR (qualitative) after 6 months during treatment (p<0.05). Two patients (one with low and another with moderate viral load) had achieved SVR (p>0.05). These two patients had respectively mild and moderate hepatitis (p>0.05).

Seventeen patients (85%) had leucopoenia (4 patients had WBC 3.4×10^9/l, 13 patients had WBC 2.3×10^9/l) and 3 patients (15%) had thrombocytopoenia (<150×10^9/l) during current treatment. On reviewing these patients' previous CBC results while they were on regular interferon combination therapy, it was found that 6 of them (30%) had leucopoenia (5 patients had WBC 3.4×10^9/l,

Table 1. *Comparison of responses to treatment with pegyalated and non-pegylated interferons*

Drug used	Number of patients who responded		
	ETR	SVR	SBR
Interferon and ribavirin	4 (20%)	0	0
Pegylated interferon and ribavirin	7 (35%)	2 (10%)	1 (5%)

ETR: End of treatment response
SVR: Sustained virologic response
SBR: Sustained biochemical response

and one had $2.3 \times 10^9/l$) and none had thrombocytopoenia (P>0.05).

One patient was hypothyroid on replacement therapy from previous interferon treatment; however l-thyroxin requirement of this patient did not increase during the current treatment with pegylated interferon and ribavirin. None of the other patients developed denovo thyroid dysfunction. None of the patients experienced significant subjective constitutional symptoms with the current therapy as compared to previous therapy of regular interferon-ribavirin combination.

DISCUSSION

Since the discovery of HCV, treatment of patients chronically infected with this virus was continuously modified to achieve higher response rates. Several variables were found to affect treatment response, including age at infection, gender, viral load, virus genotype, stage of liver fibrosis and patient's immunity status.[4,5,10–13] Iron overload was found to decrease patient response to treatment; however iron reduction via phlebotomy did improve the response.[14,15] Response to treatment in HCV patients is assessed by the normalisation of liver enzymes and decrease in viral load beyond detection level (qualitative HCV RNA PCR <100 copies/ml). Hence non-responders and relapsers represent the same group of patients where both groups have persistent viraemia at end of treatment with the difference in the load being above or below detection level depending on the test used. With the improvement of viral load assays with lower limit detection level, more cases of true non-responders rather than relapsers should be diagnosed in future. Non-responders or relapsers to old treatment regimen have been candidates in different controlled studies for new regimens to improve their response as compared to naïve patients. Extended and higher dose treatment with interferon monotherapy was associated with decreased relapse rate and sustained response rate in 20–40% of cases.[16] Introduction of combination therapy was more effective than interferon monotherapy in naïve patients. However, results were disappointing with re-treatment in patients who did not respond to initial interferon monotherapy (3–29%) and was associated with sustained response in 46–58% in selected group of relapsers.[17–19] Viral mutation and development of quasispecies in response to standard interferon regimen together with pre-treatment patients and viral demographics may explain the response failure in the majority of patients infected with HCV to interferon monotherapy or combination therapy (>50%).[20] Long-acting pegylated interferon, which is associated with constant levels between consecutive doses, was found to be more effective than regular interferon in naïve patients.[6-9] In our study, more patients had ETR with pegylated interferon combination therapy as compared to previous regular interferon combination therapy (7 versus 4 patients). This effect was influenced by the viral load (p<0.05) rather than by the degree of fibrosis (p=0.056). Unfortunately this response was not durable after stopping treatment where only 2 patients (10%) had SVR and 5 patients relapsed off treatment (71.4%). SVR was only achieved in a subset of patients that had viral load below detectable level with previous standard combination therapy (Relapsers). This additional effect of pegylated interferon is probably through decreasing viral mutation or development of less quasispecies strains. Though pegylated interferon was slightly superior to regular interferon in this group of patients, this effect is modest since it does not change most of pre treatment host and viral factors that also influence patient response.

In a similar study by Afdahl *et al* using pegylated interferon alfa-2a plus ribavirin only preliminary ETR was reported. ETR was 61% in relapsers and 25% in non-responders.[21] Different other combinations were used with pegylated interferon including mycophenolate mofetil and amantadine. The highest ETR reported was 71% in relapsers and 40% in non-responders upon adding amantadine to pegylated interferon and ribavirin.[21] In our study ETR was 100% in Relapsers and 18.7% in Non-responders, however SVR was 50% in Relapsers and 0% in Non-responders.

Other dugs have been used as adjuvant or alternative therapy including ursodeoxycholic acid,[22] non-steroidal anti inflammatory drugs,[23] thymosin,[24] ISIS 14803 (anti-sense therapy),[25] histamine dihydrochloride (Maxamine)[26] and interlukins 10 and 12,[27,28] none of them improved viral response rates. New investigational agents such as proteinase inhibitors, Albuferon, VX-497 and ribozyme therapy may prove to be beneficial in future.[29–31]

Currently there is no solid consensus regarding treatment of non-responders or relapsers after standard interferon-ribavirin combination therapy. However it seems that relapsers may benefit from pegylated interferon combination therapy. Further studies are required to assess whether prolonged or maintenance pegylated interferon alone or in combination with other anti viral agents can improve response in this group of patients.

CONCLUSION

This study suggests that therapy with pegylated interferon in combination with ribavirin may be beneficial in patients with HCV who relapsed after initially clearing HCV RNA during previous treatment with standard interferon-ribavirin combination therapy. Patients with persistent viral load during previous standard combination therapy are unlikely to respond to pegylated interferon-ribavirin combination therapy and should be enrolled in more clinical trials with different drugs and regimen to achieve a better response.

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