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Daily consensus interferon (CIFN) monotherapy in non-responders or relapsers to a previous interferon regime: One year follow-up after 48 weeks of treatment

‹nterferon tedavisine cevaps›z veya nükseden hastalarda günlük konsensus interferon (CIFN) monoterapisi: 48 haftal›k tedavi sonras› 1 y›ll›k izlem

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Background/aims: *Data suggests on the basis of thrice a week therapy, efficacy of mono consensus interferon is comparable to other alpha interferons. One-year follow-up after 12-month daily consensus interferon monotherapy for chronic hepatitis C among non-responders or relapsers to previous consensus interferon monotherapy is investigated.* ***Methods:*** *Between February and August 1998, 11 non-cirrhotic patients with previous consensus interferon failure were treated. Six were relapsers and five non-responders. Serum HCV-RNA was tested at the 12th and 48th weeks of treatment and followed for one year thereafter.* ***Results:*** *Eight (72%) were HCV-RNA negative at both 12th and 48th weeks. Of these, 60% (3/5) were among previous non-responders and 83% (5/6) were among previous relapsers. One year sustained virological response was 55%. Of this, 40% (2/5) were among non-responders and 66% (4/6) previous relapsers.* ***Conclusions:*** *These findings suggest that daily consensus interferon needs to be further investigated as an alternative to pegylated formulations, especially with the addition of ribavirin.*

Amaç: *Konsensus interferon monoterapisi ile ilgili veriler, konsensus interferon monoterapisinin haftada 3 kez verilen diğer alfa interferonlarla kıyaslanabilecek etkinlikte olduğunu göstermektedir. Bu çalışmada daha önce interferon-alfa monoterapisi alan ve tedavi sonrası cevapsız veya relaps olan HCV'li olgulara 12 ay süre ile günlük konsensus interferon tedavisi sonrası bir yıllık sonuçları değerlendirildi.* ***Yöntem:*** *Önceki alfa-interferon tedavisi sonrası cevap verip nüks gelişen veya cevapsız 11 non-sirotik HCV olgusu bir yıl sure ile konsensus interferonla tedavi edildi. Serum HCV-RNA düzeyleri 12., 48. hafta ve tedavi bitiminden bir yıl sonra yeniden değerlendirildi.* ***Bulgular:*** *Konsensus interferonla tedavi edilen olgularda HCV-RNA olguların 8'inde (%72) hem 12. hem de 48. haftalarda negative bulundu. Bu olguların %60'ı (3/5) önceki alfa-interferon monoterapsine yanıtsız, %83'ü (5/6) relaps gösteren olgulardı. Bir yıllık kalıcı cevap oranı %55 idi. Kalıcı cevap veren olguların %40'ı önceki alfa-interferon monoterapisine yanıtsız, %66'sı (4/6) relaps gösteren olgulardı.* ***Sonuç:*** *Bu bulgular konsensus interferon tedavisinin pegylated interferonlara alternatif olabilmesi için konsensus interferon, ribavirin kombinasyonu ile ileri çalışmalar yapılması gerektiğini göstermektedir.*

Key words: Chronic hepatitis C, daily consensus interferon, sustained virologic response

Anahtar kelimeler: Kronik hepatitis C, günlük konsensus interferon, kal›c› viral cevap

INTRODUCTION

Hepatitis C virus (HCV) infection is universally common and potentially highly progressive in most cases. Chronic HCV has been associated with the development of severe liver disease including cirrhosis and hepatocellular carcinoma (1). It is estimated that more than four million Americans are affected, as well as a total of 170 million individuals worldwide (2, 3). Until recently, interferon-alpha (IFN-α) was the only available therapy for patients with chronic hepatitis C (4, 5). Interferons are a family of cytokines with antiviral and immunomodulatory properties (6). However, more than half of the patients treated with alpha interferons do not respond to treatment and among

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those who do respond, approximately two thirds will relapse within six months of discontinuation of the therapy (7, 8). Thus, overall sustained response rate to IFN-α therapy is approximately 15-20% (9). One potential option is to re-treat these patients with a different interferon or with the same interferon at a higher dose or for a longer duration. Indeed, a number of investigators have examined these therapeutic approaches among non-responders and relapsers. IFN-α retreatment in prior non-responders has been found to be ineffective. Alberti et al. reported a 1-2% sustained response rate in this group of patients (10). Results for relapsers, following retreatment for up to one year, are a little better but not satisfactory, with sustained response rates of 0%-53% (11-12). Peginterferon has recently become available for the treatment of patients who were non-responders or relapsers to either IFN monotherapy or IFN and ribavirin combination. In one study, 17 non-responders to IFN monotherapy and 84 non-responders to IFN and ribavirin were retreated with peginterferon-α 2b and ribavirin. Overall, sustained virologic response (SVR) occurred in 25% of patients treated with a higher dose of peginterferon (1.5 mg/kg/week) and lower dose of ribavirin (800 mg/day) and in 40% of patients treated with a lower dose of peginterferon (1 mg/kg/week) and higher dose of ribavirin (1000-1200 mg/day) (13). Peginterferon and ribavirin retreatment of patients who relapsed after initial treatment with IFN and ribavirin achieved 60% SVR (13).

Consensus interferon (CIFN; Amgen Inc., Thousand Oaks, CA, currently: InterMune, Inc., Brisbane, CA) is a genetically engineered molecule derived by assigning the most commonly observed amino acid of several natural IFN-α subtypes to develop a novel type 1 IFN (14, 15). In preliminary trials, CIFN has been shown to be effective in naive patients, in patients who have either not responded to previous interferon therapy or relapsed after discontinuation of interferon therapy and in those with viral breakthroughs with a good safety profile (16, 17). Preliminary HCV kinetic and clinical studies have suggested that daily interferon is more advantageous than twice in a week administration (18, 19, 20). There is limited data available about daily use of CIFN. Our study investigated the efficacy of long-term (12 month) daily CIFN therapy for chronic hepatitis C patients who have either relapsed or were non-responders to previous interferon therapy. At the time of the study, no pegylated formulations of interferon/ribavirin combinations were available.

Our initial experience with daily CIFN among non-responders and relapsers was previously reported (21). At the end of the 12-month treatment period, 60% of the non-responders and 83% of the relapsers were negative for serum HCV-RNA. We hereby report our one-year follow-up of these patients.

MATERIALS AND METHODS

Between February and August 1998, a total of 11 patients with a mean age of 45 ± 9.8 years, in whom previous interferon monotherapy failed, were enrolled with an intent-to- treat protocol. None of these patients had evidence of cirrhosis in their liver biopsies. There were seven females and four males, five of whom were non-responders and six relapsers.

The protocol consisted of administration of 15 mcg daily of CIFN for the initial eight weeks, to be followed by a 9 mcg daily dose for the following 10 months to complete a one-year treatment plan. Serum samples were drawn weekly for the first month and monthly thereafter for biochemical analysis as well as complete cell count.

Serum HCV-RNA was initially tested at the 12th week, at the end of the 48-week treatment period, as well as at one year following the completion of treatment. HCV genotypes were not obtained.

RESULTS

Four patients (44%) needed dose reduction to 9 mcg before the end of eight weeks of treatment due to of fatigue and/or leukopenia. Three other patients suffered from fatigue, but it was tolerable and no worse than their previous experience with interferon treatment. All 11 patients completed the one-year treatment regimen and were evaluated for virological response. Results are summarized in Table 1. Overall, eight (72%) patients became serum HCV-RNA negative at the end of 48 weeks. Of these, 60% (3/5) were among previous non-responders and 83% (5/6) were among previous relapsers. All patients who became HCV-RNA negative at the end of the treatment were also HCV-RNA negative at the 12th week. One year after completion of treatment, overall 55% (6/11) were still negative. Of these, 40% (2/5) were among previous non-responders and 66% (4/6) were among previous relapsers.

Table 1. Daily use of consensus interferon (CIFN): One-year follow-up after 48 weeks treatment period

	Total (n=11)	Nonresponder (n=5)	Relapser (n=6)
HCV-RNA negativity 12th week	72% (8/11)	60% (3/5)	83% (5/6)
HCV-RNA negativity 48th week	72% (8/11)	60% (3/5)	83% (5/6)
HCV-RNA negativity one year follow-up	55% (6/11)	40% (2/5)	66% (4/6)

HCV-RNA: Hepatitis C virus RNA

DISCUSSION

Chronic hepatitis C is an insidious infection that may progress to cirrhosis in approximately 25% of patients with chronic HCV infection (2). The rate of progression from chronic hepatitis to cirrhosis is approximately 1-4% per year (22). Fifteen to 30% of the liver transplantations performed in the United States are for complications associated with chronic hepatitis C (23). Thus, patients needed to be treated in early phases in an attempt to reduce the progression of the disease to cirrhosis.

Preliminary hepatitis C virus kinetic and clinical studies have suggested that daily interferon is more advantageous than TIW administration (18, 19, 20). This has ultimately led to the development of pegylated formulations. Management of chronic hepatitis C patients resistant to previous interferon therapy is a challenging problem; retreatment with IFN-α of prior non-responders has been reported to be ineffective (0%-4%)(17). By comparison, retreatment of non-responders with 15 mcg of CIFN three times a week for 48 weeks is associated with a SVR rate of 13% (17).

In a multicenter study, it was shown that 9 mcg of CINF and 3 MIU INF-α 2b had a comparable effect in both early and sustained response rates (18). In another study, 15 mcg TIW dose of CIFN among patients who were relapsers or non-responders showed HCV-RNA clearance rates of 25% and 3%, respectively (24).

Although the reason for the better response rate observed with CIFN monotherapy is not clear, three factors might be important in its explanation. i) Possible decrease in viral load after the first unsuccessful therapeutic trial could be a contributing factor. ii) CIFN is also known to have a different structure from that of IFN-α. Indeed, CIFN was reported as a more effective drug for treatment, particularly in patients with HCV genotype 1 (25). iii) CIFN has a 10-fold increased affinity for the type 1 interferon receptor compared to IFN-α 2a or 2b (26). Recent data from Reddy et al. suggests that daily or twice daily administration of CIFN is needed to achieve sustained serum HCV-RNA suppression in genotype 1 patients (27).

Serum HCV-RNA concentration is a better indicator of viral eradication than serum alanine aminotransferase (ALT) values (28). Reports have indicated that achievement of viral clearance after the 12th week of interferon and CIFN therapy is highly predictive of subsequent biochemical and virologic response (29, 30). Patients who achieve response to re-treatment with 15 mcg of CIFN demonstrate an ALT and HCV-RNA response by at least week eight of re-treatment (17). It has been observed that a 24-week SVR is generally conserved at least at the end of the 48th week of treatment (31). Thus, early viral clearance is a good indicator of long-term result and possible sustained response. For this reason, we expected the viral clearance rate at the 12th week to be a good criterion for evaluating our patients, and our results are also compatible with others (17, 31). Our data shows that a fairly meaningful early viral response (EVR), end of treatment response (ETR) and SVR rate can be achieved with CIFN among non-responders or relapsers.

In our study, HCV-RNA clearance was much higher in patients who had relapsed after initial response than in those who had no response at all to initial interferon therapy. These results are compatible with the results suggested in the literature (17, 18, 24, 27).

Another important observation was the 40% and 66% SVR achieved among prior non-responders and relapsers, respectively. In comparison with the lower response rate in the literature, this result is noticeably different (17, 24, 27). It is necessary to determine whether this high early viral clearance rate is due to the dose and/or daily administration of interferon. Our results seemed to support others' observations (18, 27).

Some viral factors like HCV-RNA titer and HCV genotype and some host factors such as age and presence of cirrhosis also affect the response rate to interferon treatment (10, 11, 32). In our group, no patient was cirrhotic and genotype was not obtained prior to treatment.

The other important finding is tolerability to daily use of CIFN. None of the patients required discon-

tinuation of treatment. Since all the patients had tried the IFN-α treatment previously, they declared that they found it easier to tolerate CIFN, although no quantitative scoring system was used to evaluate the tolerability to treatment.

The side effects associated with CIFN treatment were comparable to those reported previously for IFN-α treatment, such as flu-like symptoms, anemia etc. (33, 34). No patients were excluded from the study due to noncompliance. Four patients (44%) needed dose reduction, mainly due to severe fatigue and leukopenia.

Although our data is limited to an 11-patient experience, preliminary data of daily CIFN use in relapsers and non-responders has provided encouraging results. It is well tolerated and not associated with an increase in the incidence of side effects.

Based on these observations, daily CIFN monotherapy can be considered to be effective in achieving SVR among patients who relapsed after standard interferon monotherapy. These results are comparable to outcomes of ribavirin and pegylated interferon combinations reported in the literature (13). In conclusion, further prospective controlled trials are warranted to study the effects of daily CIFN plus ribavirin treatment option, among PEG/ribavirin relapsers.

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