High dose consensus interferon in nonresponders to interferon alpha-2b and ribavirin with chronic hepatitis C

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OBJECTIVES: Approximately 60% of patients with chronic hepatitis C treated with a combination of interferon (IFN) alpha-2b and ribavirin are nonresponders. The purpose of the present study was to evaluate the efficacy of treatment with high dose consensus IFN (CIFN) (15 µg/day) in nonresponders.
METHODS: Patients were administered 15 µg CIFN/day. Treatment was stopped in those whose serum hepatitis C virus (HCV) RNA remained detectable at 12 weeks. Those with undetectable HCV RNA at 12 weeks continued on 15 µg three times per week for a further 36 weeks.
RESULTS: Twenty-four patients were recruited; six (25%) withdrew before 12 weeks because of side effects. Of the 18 patients who completed 12 weeks of therapy, nine (38%) had undetectable HCV RNA. Seven of nine patients who were HCV RNA-negative at week 12 completed 48 weeks of treatment and two withdrew because of intolerable side effects. At 48 weeks, HCV RNA remained undetectable in three patients. After six months of follow-up off treatment, two patients (8%) continued with no detectable HCV RNA in their sera.
CONCLUSIONS: High dose induction therapy with CIFN 15 µg/day in prior nonresponders to IFN alpha-2b and ribavirin led to loss of detectable HCV RNA in 50% of patients, but this response was only sustained in 8% of patients on completion of therapy.

Key Words: *Hepatitis B; Interferon; Nonresponders; Sustained response*

Traitement à forte dose d'interféron consensus chez des non-répondeurs à l'interféron alfa-2b et à la ribavirine atteints d'hépatite C chronique

OBJECTIFS : Environ 60 % des patients atteints d'une hépatite C chronique traités par une association d'interféron (IFN) alfa-2b et de ribavirine sont non-répondeurs. L'objectif de la présente étude consiste à évaluer l'efficacité du traitement par l'IFN dit consensus (CIFN) à forte dose (15 mg/jour) chez les non-répondeurs.
MÉTHODES : On a administré aux patients 15 mg de CIFN/jour. Le traitement a été interrompu chez ceux dont l'ARN du virus de l'hépatite C (VHC) du sérum demeurait décelable au bout de 12 semaines. Les patients dont l'ARN du VHC se situait sous le seuil de détection au bout de 12 semaines ont continué à recevoir 15 mg trois fois par semaine pendant 36 semaines additionnelles.
RÉSULTATS : Vingt-quatre patients ont été recrutés; six (25 %) se sont retirés avant 12 semaines en raison d'effets secondaires. Parmi les 18 patients qui ont complété les 12 semaines de traitement, neuf (38 %) avaient une concentration d'ARN du VHC sous le seuil de détection. Sept des neuf patients chez qui l'ARN du VHC était négatif au bout de 12 semaines ont complété 48 semaines de traitement et deux patients se sont retirés en raison de réactions secondaires intolérables. Au bout de 48 semaines, l'ARN du VHC est demeuré sous le seuil de détection chez trois patients. Après six mois de suivi post-traitement, on n'a pu déceler la présence dans le sérum de l'ARN du VHC chez deux (8 %) patients.
CONCLUSIONS : Un traitement d'induction à forte dose de CIFN 15 mg/jour chez des patients antérieurement non répondeurs à l'IFN alpha-2b et à la ribavirine a mené à la disparition d'ARN du VHC détectable chez 50 % des patients, mais cette réponse n'a été soutenue que chez 8 % des patients au terme du traitement.

Hepatitis C virus (HCV) is a single-stranded, positive-sense RNA virus belonging to the Flaviviridae family (1). Fifty per cent to 80% of people infected develop a chronic infection (2-4). A proportion of patients ultimately develop cirrhosis and hepatocellular carcinoma. The lifetime risk of cirrhosis in an HCV carrier is about 20% but may be higher depending on the presence of risk factors recognized to promote fibrosis. The rate of development of liver failure in patients with cirrhosis due to HCV ranges from 25% at five years (5) to 25% at 10 years (6).

Treatment of HCV to date has involved the use of interferons (IFNs), which have both immunomodulatory and antiviral properties. Standard IFN alpha monotherapy results in a sustained virological response ranging from 6% to 25%, depending on both the dose and the duration of therapy, and the viral and host factors. The addition of the nucleoside analogue ribavirin to standard IFN alpha-2b improves the overall sustained virological response to 43%, and this combination of therapy has been the standard of care (7-11). Recent data indicate that long acting pegylated IFNs in combination with ribavirin have an overall sustained virological response of 54% to 56% when given to treatment-naïve patients (12). There are no published data on the efficacy of pegylated IFN and ribavirin in prior nonresponders to IFN alpha-2b and ribavirin.

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TABLE 1
Demographic profile at the start of consensus interferon treatment

n	24
Men	20 (83%)
Age (mean)	49 years
Genotype 1	18 (75%)
Genotype 2	1 (4%)
Genotype 3	1 (4%)
Genotype 4	4 (17%)
Cirrhosis	13 (54%)
Hemoglobin (g/L)	147.6
White blood cells $\times 10^9$/L	5.76
Platelets $\times 10^9$/L	185.9
Alanine aminotransferase (U/L)	136.9
Aspartate aminotransferase (U/L)	100.7
Bilirubin (μmol/L)	13
INR	1.09
Thyroid stimulating hormone (mIU/L)	2.00

INR International normalized ratio

Consensus IFN (CIFN) is a genetically engineered molecule derived by aligning the sequences of all known alpha IFNs and assigning the most commonly observed amino acid in each sequence (13). Studies have shown that treatment of naïve subjects with HCV infection with 9 μg CIFN gives a sustained virological response similar to that of standard IFN alpha-2b, but the former is more effective in those with a high viral load and/or with genotype 1 infection (15 μg CIFN is equivalent to 3.75 MIU IFN alpha-2b) (14). Retreatment with CIFN for 12 months has been shown to be effective in achieving a sustained response of 58% in relapsers to previous IFN alpha-2b or CIFN given for six months and 13% in nonresponders to six months of prior IFN monotherapy when given for 12 months (15).

The purpose of the present study was to evaluate the efficacy of high dose CIFN (15 μg daily) induction therapy given for 12 weeks followed by CIFN (15 μg) three times per week for a further 36 weeks in patients with chronic HCV infection who were nonresponders to previous therapy with a complete course of IFN alpha-2b and ribavirin (ie, those who had received greater than 80% of the recommended IFN alpha-2b and greater than 80% of the recommended dose of ribavirin for their body weight for 80% of the recommended duration of therapy). It was hypothesized that CIFN given in a daily dose would be able to achieve a greater antiviral effect by achieving higher serum concentrations, allowing for less chance of viral breakthrough and development of viral resistance during therapy.

METHODS

Study design

Patients were selected from our department of medicine database. To be eligible for the study, patients had to have detectable HCV RNA in their serum and persistently elevated serum alanine aminotransferase levels at least 1.5 times the upper limit of normal. Eligible patients also had to have completed a full course of IFN alpha-2b and ribavirin therapy. Patients were excluded if they had a history of severe, untreatable depression; HIV coinfection; current alcohol or illicit drug use; uncontrolled seizure disorder; evidence of decompensated liver disease; or a thyroid abnormality in which thyroid function could not be maintained with the appropriate medication. Previous nonresponsiveness was defined as detectable HCV RNA after receiving a full three-month course of treatment. Patients who initially responded to treatment but subsequently relapsed after therapy was stopped were not included in the study. The study was approved by the University Health Network Ethics Committee, and all participating patients gave their informed written consent. Baseline laboratory parameters included hemoglobin, white blood cell count, platelet count, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, HCV RNA (qualitative), bilirubin, albumin, thryoid stimulating hormone and international normalized ratio. Testing for HCV genotypes was conducted.

TABLE 2
Reasons for withdrawal of therapy

Patient number	Reason for withdrawal
1	Low neutrophils, headache
2	Fatigue, myalgias
3	Uncontrollable glucose
4	Confusion
5	Fatigue, generally unwell
6	Fatigue, fever

Patients were to receive 15 μg CIFN daily for the first three months when a qualitative HCV RNA test was done. Patients with persistently detectable HCV RNA at week 12 had their treatment stopped. Those with undetectable HCV RNA were to continue treatment at a dose of 15 μg subcutaneously three times per week for a further 36 weeks. CIFN was to be stopped at week 48 and HCV RNA levels measured at this time. Repeat testing for HCV RNA was to be performed six months after stopping CIFN therapy.

Identification of genotypes

HCV genotypes were identified through a modification of the specific line probe assay (Inno-LiPA system, Innogenetics NV, Belgium) (16).

Serum HCV RNA

HCV RNA qualitative testing was performed at baseline, and at weeks 12, 48 and six months after termination of CIFN therapy using the second generation Roche Amplicor qualitative assay (Roche Diagnostics Corporation, USA), lower limit of detection 50 IU/mL. End-of-treatment responders were defined as those with undetectable serum HCV RNA at the end of 48 weeks of treatment. Sustained virological responders were those with undetectable HCV RNA at 48 and 72 weeks.

RESULTS

There were 24 patients enrolled in the study; 20 (83%) of the patients were male. The mean age of patients was 49 years. The HCV genotype distribution in the 24 patients was genotype 1, 18 patients (75%); genotype 2, one patient (4%); genotype 3, one patient (4%); and genotype 4, four patients (17%). Thirteen patients (54%) had cirrhosis on pretreatment liver biopsy (Table 1).

Six patients (25%), all of whom were cirrhotic, withdrew from the study before completing 12 weeks of CIFN therapy because of severe, intolerable side effects (Table 2). Of the

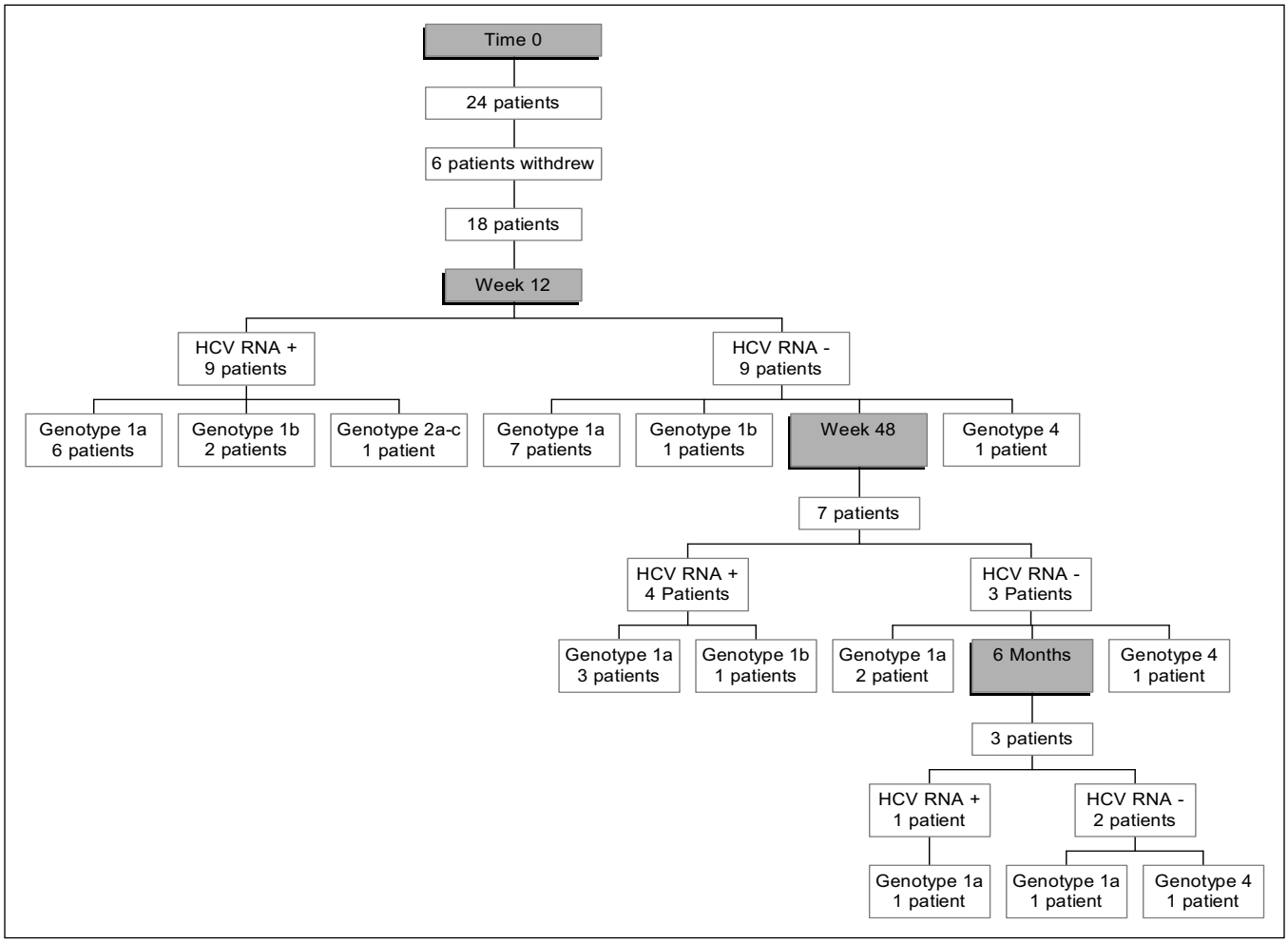

Figure 1) *Response to consensus interferon according to hepatitis C virus (HCV) genotype*

18 patients who completed 12 weeks of therapy, nine (38%) had undetectable HCV RNA at the time and, thus, continued with treatment (Figure 1). Seven of these nine patients completed 48 weeks of treatment and two patients withdrew, again because of intolerable side effects (ie, fatigue in one patient, and fatigue, myalgias and arthralgias in the other). At 48 weeks of treatment, three patients remained with undetectable HCV RNA in their serum. After a six-month follow-up, two patients (8%) had a sustained virological response.

Of the three patients who had undetectable HCV RNA after 48 weeks of treatment, two had had a genotype 1 infection and the other genotype 4. The virological response rates according to HCV genotype are shown in Figure 1. A sustained virological response was achieved in two patients – one genotype 1 and the other genotype 4. The genotype 1 sustained responder had cirrhosis.

DISCUSSION

As expected, our patient population of nonresponders to IFN alpha-2b and ribavirin had characteristics typical of those with a poor response to antiviral therapy (ie, genotypes 1 and 4, cirrhosis on liver biopsy and male sex). The present study indicates that some patients with hepatitis C infection, although resistant to full doses of standard IFN alpha-2b plus ribavirin, may respond to high dose CIFN monotherapy.

Earlier studies have shown that patients who failed six months of standard IFN alpha-2b or CIFN monotherapy could achieve a sustained virological response when retreated with CIFN, three times a week, for 12 months rather than six months, with a sustained virological response rate of 13% in previous nonresponders (15).

Few studies have reported the efficacy of retreatment of nonresponders to previous full dose combination therapy with IFN alpha and ribavirin, and none have employed high dose standard IFN monotherapy in this situation. One study added the antiviral amantadine to retreatment with IFN alpha-2b and ribavirin in previous nonresponders to IFN alpha-2b and ribavirin and achieved a strikingly high (57%) sustained virological response rate (17). Other studies with modified protocols unfortunately have not been able to repeat these excellent results (18,19). The addition of other nonantiviral agents (eg, ursodeoxycholic acid) yields a higher biochemical but not an enhanced virological response (20,21). An alternative approach is not to attempt virological cure, but rather to minimize the long term effect of inflammation caused by the virus (ie, fibrosis). This was achieved in a short course (90 days) of interleukin-10, but no long term studies using this agent have been reported (22).

The high dose therapy with CIFN, given during the initial 12-week induction phase in the present study, had a high side

effect profile. The symptoms precipitating withdrawal from CIFN therapy in the present group of highly motivated patients were systemic, namely weakness, irritability and, in one patient, profound confusion. These side effects were maximal during the first three months during the 'induction' period and disappeared in all patients within one week of treatment cessation. Although dosing was daily, the short half-life of standard IFN causes wide fluctuations in serum IFN levels; the sudden troughs in serum concentrations of IFN are likely responsible for the severe 'flu-like symptoms . These symptoms may be less with the more constant serum IFN levels provided by pegylation. Of the six patients who withdrew before receiving three months of treatment, all six (100%) had documented cirrhosis. In patients with hepatitis B virus treated with IFN, more psychiatric side effects have been observed in patients with cirrhosis (23).

In the present study, one-half of patients who had undetectable HCV RNA after induction therapy had a virological breakthrough as soon as CIFN, three times weekly, was administered after week 12. If viral replication had been continually suppressed for longer, it is conceivable that a greater sustained virological response could have been achieved. Because of the high side effect profile of high dose CIFN, this was unfeasable. The addition of oral ribavirin to INF therapy markedly reduces the relapse rate and, thus, enhances the antiviral response to IFN drug therapy (10,11).

The present pilot study shows that in a population of nonresponders to full-dose IFN alpha-2b plus ribavirin, loss of detectable virus with high dose daily CIFN is possible in one-half of patients. Thus, it is postulated that if high serum concentrations of IFN can be maintained with fewer side effects, as is possible with pegylated IFN, it may be reasonable to use this modified IFN to retreat nonresponders to standard IFN alpha-2b and ribavirin.

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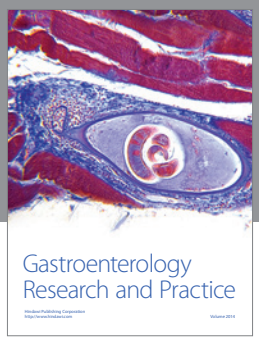

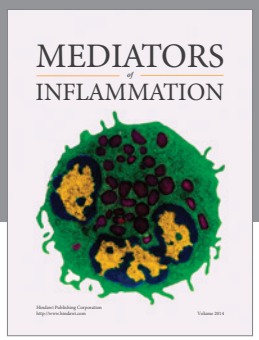

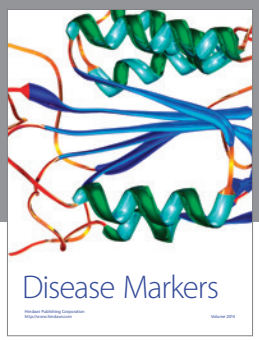

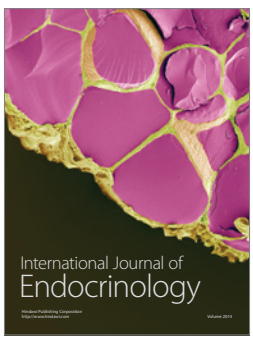

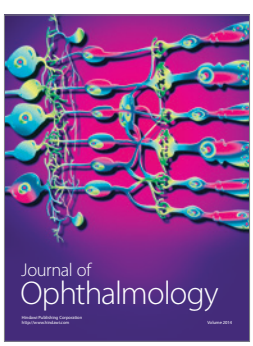

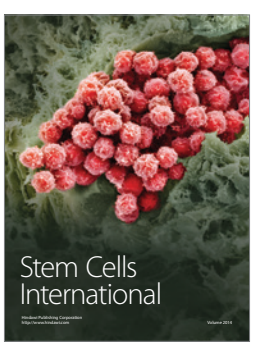

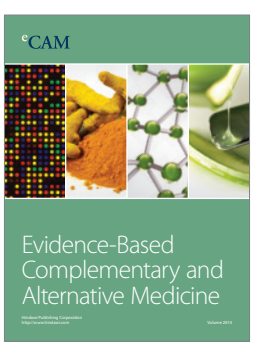

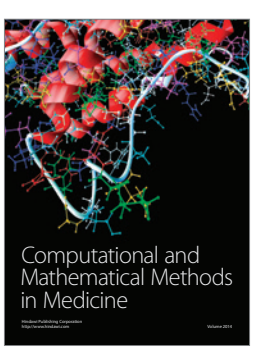

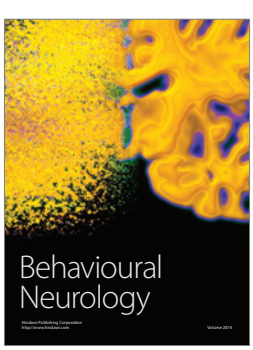

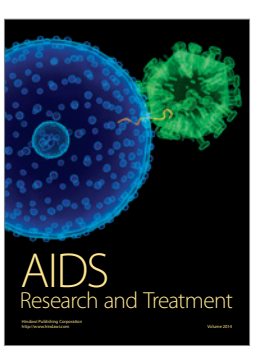

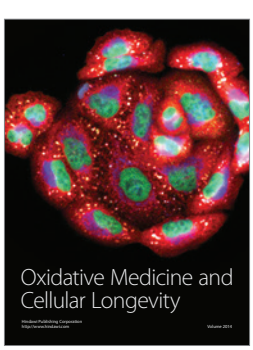

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