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

David N Moskovitz MD BSc, Pooma Manoharan MD, E Jenny Heathcote MB BS MD FRCPC

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

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-naive 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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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). 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 HCV RNA at week 12 had their treatment stopped. Those 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.

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

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Demographic profile at the start of consensus interferon treatment</th>
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<tbody>
<tr>
<td>n</td>
<td>24</td>
</tr>
<tr>
<td>Men</td>
<td>20 (83%)</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>49 years</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>18 (75%)</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>13 (54%)</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>147.6</td>
</tr>
<tr>
<td>White blood cells × 10⁹/L</td>
<td>5.76</td>
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<tr>
<td>Platelets × 10⁹/L</td>
<td>185.9</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>136.9</td>
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<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>100.7</td>
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<tr>
<td>Bilirubin (µmol/L)</td>
<td>13</td>
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<tr>
<td>INR</td>
<td>1.09</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (mIU/L)</td>
<td>2.00</td>
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</tbody>
</table>

INR International normalized ratio

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Reasons for withdrawal of therapy</th>
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<tbody>
<tr>
<td>Patient number</td>
<td>Reason for withdrawal</td>
</tr>
<tr>
<td>1</td>
<td>Low neutrophils, headache</td>
</tr>
<tr>
<td>2</td>
<td>Fatigue, myalgias</td>
</tr>
<tr>
<td>3</td>
<td>Uncontrollable glucose</td>
</tr>
<tr>
<td>4</td>
<td>Confusion</td>
</tr>
<tr>
<td>5</td>
<td>Fatigue, generally unwell</td>
</tr>
<tr>
<td>6</td>
<td>Fatigue, fever</td>
</tr>
</tbody>
</table>

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, untreated depression; HIV co-infection; 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, thyroid stimulating hormone and international normalized ratio. Testing for HCV genotypes was conducted.

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.

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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 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-2b 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 unfeasible. 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 non-responders 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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REFERENCES
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