# Early prediction of nonresponders to treatment with interferon alpha-2b and ribavirin in patients with chronic hepatitis C

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**BACKGROUND:** Treatment of chronic hepatitis C virus (HCV) infection with interferon alpha-2b and ribavirin is costly in terms of side effects, medical resources and drug costs. Furthermore, less than 50% of patients overall have a sustained virological response (SVR).
**OBJECTIVE:** To determine if the log fall in HCV RNA between baseline and week 1 (b-wk1) and between baseline and week 4 (b-wk4) after starting treatment could identify the nonresponders.
**PATIENTS AND METHODS:** Sixty-three patients who had completed a full course of therapy were identified. Quantitative measurements of HCV RNA were analyzed from stored sera, collected prospectively.
**RESULTS:** SVR was achieved in 47.1% and 47.3% of patients in the b-wk1 and b-wk4 groups, respectively. No patients had an SVR with a fall in HCV RNA of less than 0.35 $\log_{10}$ and 1.05 $\log_{10}$ at week 1 and week 4, respectively. This accounted for 44.4% and 51.7% of the nonresponders in the b-wk1 and b-wk4 groups, respectively. Once the decline in viral load was known, genotype, age, sex and baseline viral load did not provide additional power in predicting treatment responses.
**CONCLUSION:** A fall of 1.05 $\log_{10}$ in HCV RNA at week 4 predicts those patients who will not respond, identifying one-half of all nonresponders; this allows therapy to be stopped early, without depriving any patient who would have an SVR from treatment.

**Key Words:** *Hepatitis C virus; Interferon; Nonresponders; Prediction; Ribavirin; Treatment response*

## La prévision précoce des non-répondants au traitement à l'interféron alpha-2b et à la ribavirine chez les patients atteints d'hépatite C chronique

**HISTORIQUE :** Le traitement de l'infection au virus de l'hépatite C (VHC) chronique par l'interféron alpha-2b et la ribavirine s'associe à énormément d'effets secondaires, de ressources médicales et de frais de médicaments. De plus, moins de 50 % de l'ensemble des patients présentent une réponse virologique soutenue (RVS).
**OBJECTIF :** Déterminer si la chute du log de VHC-ARN entre le début du traitement et la semaine 1 (d-s1) et entre le début du traitement et la semaine 4 (d-s4) permet de repérer les non-répondants.
**PATIENTS ET MÉTHODOLOGIE :** Soixante-trois patients qui avaient terminé un traitement complet ont été sélectionnés. Des mesures quantitatives du VHC-ARN ont été analysées à partir de sérum entreposé, recueilli de manière prospective.
**RÉSULTATS :** Une RVS a été obtenue chez 41,7 % et 47,3 % des patients des groupes d-s1 et d-s4, respectivement. Aucun patient ne présentait une RVS associée à une chute du VHC-ARN inférieure à 0,35 $\log_{10}$ et à 1,05 $\log_{10}$ la semaine 1 et la semaine 4, respectivement. Ainsi, ces résultats représentent 44,4 % et 51,7 % des non-répondants au sein des groupes d-s1 et d-s4, respectivement. Lorsque la diminution de la charge virale était connue, le génotype, l'âge, le sexe et la charge virale au début du traitement ne permettaient pas de prévoir les réponses au traitement avec plus d'exactitude.
**CONCLUSION :** Une chute de 1,05 $\log_{10}$ du VHC-ARN la semaine 4 permet de prévoir les patients qui ne réagiront pas, c'est-à-dire de repérer la moitié de tous les non-répondants. Ainsi, le traitement peut être abandonné rapidement, sans priver les patients qui auraient profité d'une RVS grâce au traitement.

Chronic hepatitis C virus (HCV) infection is the most common cause of chronic liver disease worldwide (1). The most widely used treatment for chronic HCV infection until now has been a combination therapy with interferon alpha-2b (IFN-α2b) and ribavirin for 24 to 48 weeks (2,3). The rate of sustained virological response (SVR), defined as an undetectable HCV RNA at 24 weeks after treatment cessation, ranges from 16% to 69% depending on viral and host characteristics (4-6). Recent data on treatment efficacy of pegylated IFN plus ribavirin for chronic HCV infection is equivocal when compared with standard IFN-α2b plus ribavirin treatment. A recent study demonstrated that pegylated INF-α2b and ribavirin was only more effective in patients with genotype 1 and a low baseline viral load when compared with treatment using standard IFN-α2b and ribavirin; there was no difference in treatment efficacy in patients with genotype 2 or 3, or genotype 1 with a high viral load (7). However, another study using pegylated INF-α2a plus ribavirin indicated a small increase in efficacy over standard IFN-α2b and ribavirin in patients with both genotype 1 and non-1, and with both a high and a low viral load (8). Thus, it remains to be established whether the more expensive long-acting IFN plus ribavirin is

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cost effective to treat all patients with chronic HCV infection when compared with standard IFN and ribavirin.

Although it is less costly than pegylated IFN combination, combination therapy using standard IFN-α2b and ribavirin is still costly in terms of drug costs and medical resources, as well as side effects. Up to 21% of patients receiving this combination discontinue treatment before 48 weeks because of adverse side effects (4). The high rate of side effects (9,10), particularly those related to hematological parameters, demand frequent monitoring that incurs considerable time on the part of both the patients and the medical personnel. Hence, the earlier that it can be predicted which patients will ultimately fail to respond to therapy, the shorter amount of time patients would be exposed to undesirable side effects and the smaller the unnecessary financial burden on the health care system.

The prediction of treatment response to combination therapy with standard IFN and ribavirin has been reported using qualitative and quantitative analyses of HCV RNA. A positive qualitative HCV RNA test at 24 weeks identified 99% of the nonresponders to treatment, and the authors suggested treatment should only be stopped at 24 weeks if this test remained positive (11). Another study indicated that a positive qualitative HCV RNA test at week 4 identified all 35 nonresponders to IFN plus ribavirin who had previously failed to respond to IFN monotherapy; a negative qualitative test for HCV RNA in the same study identified four of five subsequent sustained virological responders (12). Using quantitative analyses of HCV RNA, a study of 25 patients published as an abstract indicated that if the fall in viral load is less than 1 $\log_{10}$ within the first week of initiating treatment, patients would ultimately not respond (13). A study using peginterferon alpha-2a plus ribavirin demonstrated that using a 2 $\log_{10}$ cutoff for fall in viral load by week 12 identified 95% of nonresponders and 65% of patients with SVR (8). A recent study combined the data from patients recruited to two large therapeutic trials that used pegylated INF and ribavirin; it was found that the lack of a 2 $\log_{10}$ fall in HCV RNA at week 12 identified 98% of nonresponders to therapy (14). These studies suggest that a quantitative analysis of the rate of decline of HCV RNA may be more sensitive and accurate in predicting treatment response than a qualitative analysis. These studies quantified the HCV RNA in copies/mL. It has been shown that HCV RNA quantified using the newly accepted standard, expressed in IU/mL, defined by the World Health Organization is more accurate and reproducible (15).

The objective of the present study was to determine if the nonresponders to treatment with IFN-α2b and ribavirin can be predicted early after starting therapy by determining the log fall in HCV RNA between baseline, week 1 and week 4. In addition, this study employed the first accepted international standard for the measurement of HCV RNA in IU/mL.

## METHODS

### Settings and interventions

All patients who had received treatment with the combination of IFN-α2b and ribavirin at the University Health Network in Toronto, Ontario, between 1998 and 2000 were reviewed. All patients were treated with IFN-α2b, 3,000,000 IU by subcutaneous injection three times per week, and ribavirin either 1000 mg or 1200 mg orally per day based on their weight (1000 mg for weight less than or equal to 75 kg and 1200 mg if more than 75 kg). The treatment duration ranged from 24 to 48 weeks. Patients were assessed at baseline and then followed at various intervals, in part, depending on their tolerance of the treatment. All patients were followed until 24 weeks after treatment cessation and the final off-treatment outcomes were known. Informed consent was obtained from each patient. Approval by the local human institutional review committee was received for this study.

Treatment outcomes were defined as nonresponders – patients who had detectable serum HCV RNA at the end of therapy by a qualitative HCV RNA analysis (greater than 50 IU/mL; for details see 'Analysis of serum HCV RNA' below); SVR – an undetectable serum qualitative HCV RNA at the end of the treatment and at 24 weeks after treatment cessation; and relapsers – patients who had a negative qualitative HCV RNA at the end of treatment but a positive result during the 24-week follow-up.

### Patients

Patients were treated if they had a positive HCV RNA at baseline, compensated liver disease and biochemical abnormalities (persistent elevation of alanine aminotransferase for six months). All patients were required to have hemoglobin 130 g/L or greater for men or 120 g/L or greater for women; white blood cell count $3\times10^9$/L or greater; absolute neutrophil count $150\times10^9$/L or greater; platelets $100\times10^9$/L or greater; prothrombin time prolonged by less than 2 s; direct bilirubin 5.1 μmol/L or less; indirect bilirubin 13.7 μmol/L or less (unless nonhepatitis-related factors such as Gilbert's syndrome were present); albumin 35 g/L or greater; creatinine 123.8 μmol/L or less; fasting blood sugar 6.4 mmol/L or less for patients without diabetes mellitus; and hemoglobin A1C 8.5% or less for patients with diabetes mellitus. All patients were human immunodeficiency virus- and hepatitis B surface antigen-negative, and had a normal serum thyroid stimulating hormone level and an antinuclear antibody titre of 1 to 160 or less. Each patient underwent a liver biopsy indicating that disease severity was more than grade 1 inflammation and grade 1 fibrosis based on the METAVIR scoring system (16).

Patients were excluded from treatment if they were over 55 years old; had any history of cardiovascular disease, hemoglobinopathy or continued alcohol and/or illicit drug use; and if there was evidence of other causes of hepatitis based on liver biopsy and patient history (such as, but not limited to, Wilson's disease, hemochromatosis, autoimmune hepatitis, significant alcohol use or obesity); and decompensated liver disease. Patients were also excluded if there was any known pre-existing medical condition that could interfere with the patient's participation. Sexually active women of childbearing potential or men would only be included if practising adequate contraception.

### Analysis of serum HCV RNA

HCV RNA measurements were performed on sera, collected prospectively, which had been separated within 6 h of collection from whole blood following centrifugation at 1000 × g for 20 min and stored at –70°C. Immediately before testing, all sera were brought to room temperature. Stored sera from baseline and week 1 and/or week 4 were available for testing in 63 treated patients. The pretreatment statuses of these 63 patients were 15 nonresponders, 24 relapsers to previous IFN monotherapy and 24 treatment-naïve patients. Quantitative analyses of HCV RNA were measured using the Cobas Amplicor HCV Monitor Test, version 2.0 (Roche Diagnostics,

USA; lower limit of detection of 600 IU/mL with a linear range of quantification between 600 and 500,000 IU/mL). Serum samples whose viral load measurements exceeded the upper limit of detection were diluted in a ratio of 1:100 using HCV-negative human plasma and retested as per the manufacturer's recommendation. The final result was then multiplied by a factor of 100 to account for the dilution. Qualitative analyses of the HCV RNA were performed using the Cobas Amplicor HCV Test, version 2.0 (Roche Diagnostics, USA). Qualitative analyses were used to determine treatment outcome because of the test's higher sensitivity (ie, lower limit of detection of 50 IU/mL). The sensitivity and precision of the Cobas Amplicor HCV Monitor Test, version 2.0 and Cobas Amplicor HCV Test, version 2.0 have recently been published (16). The variability of the quantitative assay is represented by the coefficient of variation that ranges from 18% to 33% (16). HCV genotypes were determined by Inno-Lipa HCV II test (Innogenetics NV, Belgium).

### Data and statistical analyses

For each follow-up visit (at weeks 1 and 4), the sensitivity and specificity for predicting SVR were calculated using a range of log falls in HCV RNA values as thresholds. Log fall in HCV RNA is defined as the difference between the $\log_{10}$ of HCV RNA at the beginning of treatment and the $\log_{10}$ of HCV RNA at week 1 (or 4) of treatment. The series of values (sensitivity versus 1 – specificity) were plotted to form the receiver operating characteristics (ROC) curves. The area under the curve and its standard error were calculated through the equivalence to the Mann-Whitney test statistic. The closer the area under the ROC curves to 1, the higher the predictive power of the variable for the outcome of interest. Differences between the sustained virological responders and virological nonresponders were tested using the $\chi^2$ test for dichotomous variables and the Student's *t* test for continuous variables. The independent effects of sex, genotype, age and baseline viral load in predicting the treatment response were assessed with multiple logistic regressions.

## RESULTS

### Baseline characteristics

Among the 63 patients who received treatment between 1998 and 2000, 51 patients had sera stored at baseline and at week 1, and 55 patients at baseline and at week 4. Three of 63 patients were subsequently shown to relapse; they were analyzed together with the proven nonresponders. Because the goal was to identify those who did not have an SVR, the nonresponders and relapsers shared the same treatment outcome. The baseline characteristics of these patient groups are summarized in Table 1; there was no difference in their age, sex, alanine aminotransferase levels, baseline HCV RNA levels or genotypes.

### Predictive values of the decline in HCV RNA

An SVR was achieved in 30 of 63 patients (47.6%). Of those who had a serum sample at week 1, 24 of 51 patients (47.1%) were later shown to have a sustained response. Of those who had sera stored at week 4, 26 of 55 patients (47.3%) had an SVR (Table 2). None of the patients who had a fall of less than 0.35 $\log_{10}$ (corresponding to a negative predictive value [NPV] of 1, lower limit of the 95% CI 0.76) at week 1 subsequently had an SVR. This cutoff identified 12 of 27 subsequent nonresponders (44.4%). Meanwhile, by week 4, all patients who had a fall less than 1.05 $\log_{10}$ did not respond to therapy (NPV 1, lower limit of the 95% CI 0.80). This cutoff identified 15 of the 29 nonresponders (51.7%). None of the patients with SVR had a log fall less than these specific ranges at week 1 and week 4.

The positive predictive value was equal to 1 (lower limit of the 95% CI was 0.34 and 0.57 for the baseline to week 1 [b-wk1] and to week 4 [b-wk4] groups, respectively) if the decline in HCV RNA level was greater than 2.98 $\log_{10}$ in the b-wk1 group and 3.90 $\log_{10}$ in the b-wk4 group. These cutoffs identified a response in only two of 24 (8.3%) and five of 26 (19.2%) of the sustained virological responders. Thus, the log fall in HCV RNA level is less sensitive when used to predict sustained responders than nonresponders.

The ROC curves are shown in Figure 1. They are plots of true positive (sensitivity) versus false positive (1 – specificity). The area under the ROC curve was 0.84±0.06 for the b-wk1 group and 0.90±0.04 for the b-wk4 group. This result indicates

**TABLE 1**
**Baseline characteristics of different patient groups**

| | All patients* (n=63) | Week 1 (n=51) | Week 4 (n=55) |
|---|---|---|---|
| Age, years | 44.7±1.0 | 44.8±1.2 | 44.6±1.1 |
| Sex (% male) | 66.7 | 62.7 | 67.3 |
| ALT (U/L) | 135±11 | 120±10 | 133±12 |
| HCV RNA† ($\times 10^6$ IU/mL) | 2.80±0.43 | 3.04±0.50 | 2.74±0.42 |
| Genotype (%)‡ | | | |
| 1 | 68.7 | 65.8 | 68.2 |
| Non-1 | 31.3 | 34.2 | 31.8 |

**Sixty-three patients were identified from the database: Fifty-one had sera stored at baseline and at week 1, and 55 patients had sera stored at baseline and at week 4; †Quantitative hepatitis C virus (HCV) RNA; ‡Thirteen patients in the week 1 group and 11 patients in the week 4 group did not have their genotypes determined. Non-1 includes genotypes 2a, 2b, 2c, 3, 3a and 4. Age, alanine aminotransferase (ALT) and HCV RNA are presented as mean ± SE*

**TABLE 2**
**Summary of the predictive values in log fall of hepatitis C virus (HCV) RNA**

| $\log_{10}$ fall in HCV RNA | SVR | NR | Total |
|---|---|---|---|
| **Week 1** | | | |
| Identification of NR | | | |
| ≤0.35 | 0 | 12 | 12 |
| >0.35 | 24 | 15 | 39 |
| Identification of SVR | | | |
| >2.98 | 2 | 0 | 2 |
| ≤2.98 | 22 | 27 | 49 |
| Total number of patients | 24 | 27 | 51 |
| **Week 4** | | | |
| Identification of NR | | | |
| ≤1.05 | 0 | 15 | 15 |
| >1.05 | 26 | 14 | 40 |
| Identification of SVR | | | |
| >3.90 | 5 | 0 | 5 |
| ≤3.90 | 21 | 29 | 50 |
| Total number of patients | 26 | 29 | 55 |

*NR Nonresponder; SVR Sustained virological response*

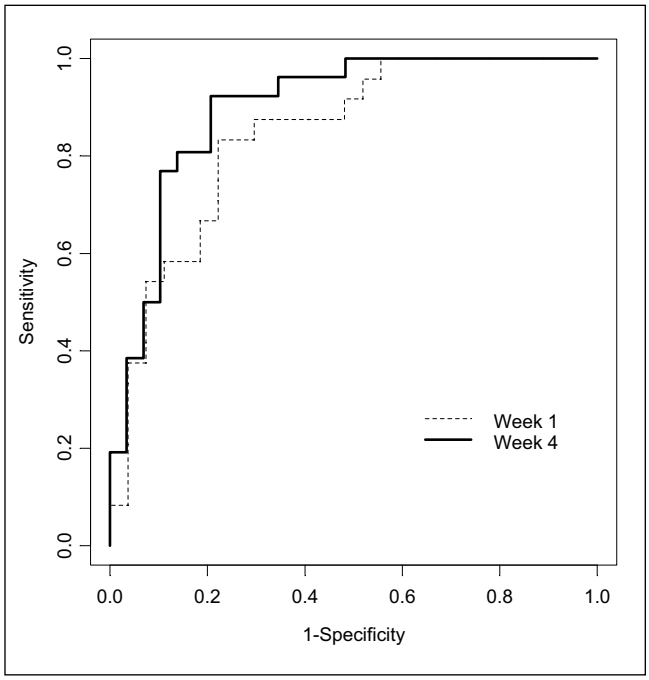


**Figure 1)** *Receiver operating characteristics (ROC) curves. ROC curves are plots of true positive (sensitivity) versus false positive (1 – specificity). The areas under the ROC curves were 0.84±0.06 and 0.90±0.04 for week 1 and week 4, respectively. An area under the ROC curve of 1 means that prediction of the outcome of interest using the evaluating variable can be made with perfect confidence. These plots illustrate that the week 4 data allows one to predict the treatment outcome with higher confidence and less variation. The cutoffs for non-responders were 0.35 $log_{10}$ and 1.05 $log_{10}$ at week 1 and week 4, respectively. The cutoffs for responders were 2.98 $log_{10}$ and 3.90 $log_{10}$ at week 1 and week 4, respectively*

that the log fall in HCV RNA level between baseline and week 4 predicts treatment outcome with higher confidence and less variability than the b-wk1 data.

**Effects of age, sex, genotype and baseline viral load**

The independent effects of age, sex, genotype and baseline viral load in predicting the treatment responses were assessed with multilogistic regression. We tested the effect of age (less than or greater than 40 years old), sex, genotype (1 or non-1) and initial viral load (two different classifications were used: less than or greater than $2\times10^6$ IU/mL, and less than or greater than $3.5\times10^6$ IU/mL. After controlling for the log fall in HCV RNA, neither age, sex, baseline viral load nor genotype was significant in predicting responses, whereas the log fall in HCV RNA was statistically significant in predicting treatment outcome after controlling for the other variables. These results indicate that once the log fall in viral load was known, age, sex, initial viral load or genotype did not independently provide additional power in predicting the treatment response.

## DISCUSSION

Our data demonstrate that quantitative analysis of HCV RNA at week 4 after starting a combination of therapy with IFN-α2b and ribavirin reliably identifies one-half of the subsequent nonresponders to this treatment regimen. None of the patients who had a fall of less than 1.05 $log_{10}$ in the HCV RNA level at week 4 had an SVR. The areas under the ROC curves and the lower limit of the 95% CI of the NPV indicate that a prediction could be made with higher confidence using the week 4 rather than the week 1 data. Changes in the HCV RNA levels predicted nonresponders more accurately than sustained responders. Our data showed that 50% of nonresponders, but less than 20% of sustained responders, could be identified at week 4. This is consistent with previous published studies suggesting that early prediction of sustained responders is difficult (11,12,14,17,18).

The coefficient of variation (CV) of the quantitative assay used in the present study ranged from 18% to 33% (19). The CV was lowest at the centre of the linear range and increased toward the upper and lower limits of the range. In our study, the mean baseline viral load was $2.8\times10^6$ IU/mL. A fall of 1.05 $log_{10}$ at week 4 corresponds to a viral load of $2.5\times10^5$ IU/mL at week 4. It is important to note that this HCV RNA level is in the middle of the linear range at week 4 (thus, the smallest CV).

The time and amount of decline in HCV RNA in predicting treatment responses is inconsistent in the literature. This could be due to the fact that different assays use different formats and have different sensitivities and units of measurement. In addition, even assays using the same unit of measurement have shown different results for the same sample (20). These shortcomings can be overcome by adopting a newly accepted standard of measurement in IU/mL defined by the First WHO International Standard for Nucleic Acid Amplification Technology Assays for HCV RNA (WHO Standard 96/790) (15). This is the first study employing this newly standardized unit in predicting treatment outcome. Hence, the amount of change in viral load reported in the present study can be compared with different studies conducted in the future that use this standardized unit.

It has been suggested that age younger than 40 years, female sex, genotype 2 or 3, absence of or only portal fibrosis, and a baseline viral load less than 2 or 3.5 million copies/mL are favorable factors in predicting a sustained response (5,20-22). Our data indicate that once the rate of decline in viral load is known, age, sex, genotype or baseline viral load did not independently provide additional power in predicting treatment outcomes. A pilot study recently suggested that a decline in the initial viral load of more than 70% within 24 h after a single dose of 5 million units of IFN-α is the only significant prognostic factor for SVR using IFN-α2b and ribavirin in patients with genotype 1 HCV infection (23). It is conceivable that the rate of fall in the viral load has incorporated these intrinsic viral and host characteristics in predicting treatment responses.

It has been observed that the degree of liver inflammation may improve (represented by a decrease in mean total histological activity index score from 2.2 to 1.7) when IFN monotherapy is continued despite the presence of detectable HCV RNA (24). However, whether this improvement in histological appearance is sustained beyond six months after cessation of IFN therapy is unknown. A recent 20-year follow-up study from Japan (25) showed improved survival following IFN therapy both in those who had an SVR and in those with only a sustained biochemical response, suggesting that in their population, continuation of treatment may provide a long term benefit in the face of sustained viremia. Improvement in quality of life (26,27) and work productivity (27), and reduced risk

for hepatocellular carcinoma (28), are seen only in patients with an SVR. Hence, the benefit of continuing patients on treatment who will not achieve SVR is questionable.

The treatment efficacy of pegylated IFN over standard IFN, when combined with ribavirin, in the treatment of chronic HCV infection for all genotypes is controversial (7,8). Not only have the optimal doses of pegylated IFN and ribavirin not been established, but their cost effectiveness in treating all genotypes needs to be addressed. A recent study examining patients with genotype 1 infection showed that peginterferon alpha-2b plus ribavirin produces a similar viral kinetic profile as IFN-α2b plus ribavirin therapy (29), suggesting that one may extrapolate our data to pegylated IFN.

Although our study is limited by its small sample size, the data strongly suggest that a prediction of treatment response, particularly of nonresponders, can be made as early as week 4 of treatment. Pegylated IFN and ribavirin will likely replace standard IFN-α2b and ribavirin. It remains to be determined whether reliable prediction of treatment outcome is possible by measuring the $\log_{10}$ fall in viral load at four weeks rather than at 12 weeks as currently published.

In conclusion, our data demonstrate that at four weeks into treatment, a drop in viral load of less than 10-fold (1.05 $\log_{10}$) from baseline guarantees subsequent nonresponse to treatment (NPV 1). A fall of less than 1.05 $\log_{10}$ identifies one-half of all nonresponders receiving the combination therapy with IFN-α2b and ribavirin for chronic HCV infection. Using this cutoff as a guide for stopping therapy would not deprive any future sustained virological responders of treatment. Hence, quantitative measurements of HCV RNA at baseline and at week 4 provide clinicians and patients with a useful tool to evaluate the risk versus the benefit of continuing or stopping therapy early. Implementation of early stopping rules would minimize side effects, drug costs, nursing and laboratory expenses but would not allow for a potential, as yet unconfirmed, long term benefit from continuing therapy in the face of persistent viremia.

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## REFERENCES


1. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: A perspective on long-term outcome. Semin Liver Dis 2000;20:17-35.
2. Canadian Association for the Study of the Liver. Canadian consensus conference on the management of viral hepatitis. Can J Gastroenterol 2000;14(Suppl B):5B-20B.
3. Booth JC, O'Grady J, Neuberger J. Clinical guidelines on the management of hepatitis C. Gut 2001;49(Suppl 1):I1-21.
4. McHutchison JG, Gordon SC, Schiff ER, et al, for the Hepatitis Interventional Therapy Group. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998;339:1485-92.
5. Poynard T, McHutchison J, Goodman Z, et al, for the ALGOVIRC Project Group. Is an "a la carte" combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? Hepatology 2000;31:211-8.
6. Heathcote J. Antiviral therapy for patients with chronic hepatitis C. Semin Liver Dis 2000;20:185-99.
7. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomized trial. Lancet 2001;358:958-65.
8. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975-82.
9. Bodenheimer HC Jr, Lindsay KL, Davis GL, et al. Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: A multicenter trial. Hepatology 1997;26:473-7.
10. Maddrey WC. Safety of combination interferon alfa-2b/ribavirin therapy in chronic hepatitis C-relapsed and treatment-naive patients. Semin Liver Dis 1999;19(Suppl 1):67-75.
11. McHutchison JG, Shad JA, Gordon SC, et al. Predicting response to initial therapy with interferon plus ribavirin in chronic hepatitis C using serum HCV RNA results during therapy. J Viral Hepat 2001;8:414-20.
12. Brouwer JT, Hansen BE, Niesters HG, et al. Early prediction of response in interferon monotherapy and in interferon-ribavirin combination therapy for chronic hepatitis C: HCV RNA at 4 weeks versus ALT. J Hepatol 1999;30:192-8.
13. Neumann AU, Dahari H, Conrad A, Pianko S, McHutchison JG. Early prediction and mechanism of the ribavirin/IFN-alpha dual therapy effect on chronic hepatitis C virus infection. Hepatology 1999;30:309A. (Abst)
14. Davis GL. Monitoring of viral levels during therapy of hepatitis C. Hepatology 2002;36(Suppl 1):S145-51.
15. Saldanha J, Lelie N, Heath A, for the WHO Collaborative Study Group. Establishment of the first international standard for nucleic acid amplification technology (NAT) assays for HCV RNA. Vox Sang 1999;76:149-58.
16. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24:289-93.
17. McHutchison J, Blatt L, Sedghi-Vaziri A, et al. Is there an optimal time to measure quantitative HCV RNA to predict non-response following interferon treatment for chronic HCV infection? J Hepatol 1998;29:362-8.
18. Wiley TE, Briedi L, Lam N, et al. Early HCV RNA values after interferon predict response. Dig Dis Sci 1998;43:2169-72.
19. Lee SC, Antony A, Lee N, et al. Improved version 2.0 qualitative and quantitative AMPLICOR reverse transcription-PCR tests for hepatitis C virus RNA: Calibration to international units, enhanced genotype reactivity, and performance characteristics. J Clin Microbiol 2000;38:4171-9.
20. Trepo C. Genotype and viral load as prognostic indicators in the treatment of hepatitis C. J Viral Hepat 2000;7:250-7.
21. Civeira MP, Prieto J. Early predictors of response to treatment in patients with chronic hepatitis C. J Hepatol 1999;31(Suppl 1):237-43.
22. Kaserer K, Fiedler R, Steindl P, et al. Liver biopsy is a useful predictor of response to interferon therapy in chronic hepatitis C. Histopathology 1998;32:454-61.
23. Jessner W, Gschwantler M, Steindl-Munda P, et al. Primary interferon resistance and treatment response in chronic hepatitis C infection: A pilot study. Lancet 2001;358:1241-2.
24. Shiffman ML, Hofmann CM, Sterling RK, et al. A randomized, controlled trial to determine whether continued ribavirin monotherapy in hepatitis C virus-infected patients who responded to interferon-ribavirin combination therapy will enhance sustained virologic response. J Infect Dis 2001;184:405-9.
25. Shindo M, Hamada K, Oda Y, et al. Long-term follow-up study of sustained biochemical responders with interferon therapy. Hepatology 2001;33:1299-302.
26. Fontana RJ, Moyer CA, Sonnad S, et al. Comorbidities and quality of life in patients with interferon-refractory chronic hepatitis C. Am J Gastroenterol 2001;96:170-8.
27. McHutchison JG, Ware JE Jr, Bayliss MS, et al. The effects of interferon alpha-2b in combination with ribavirin on health related quality of life and work productivity. J Hepatol 2001;34:140-7.
28. Yoshida H, Shiratori Y, Moriyama M, et al, for the Inhibition of Hepatocarcinogenesis by Interferon Therapy Study Group. Interferon therapy reduces the risk for hepatocellular carcinoma: National surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. Ann Intern Med 1999;131:174-81.
29. Buti M, Sanchez-Avila F, Lurie Y, et al. Viral kinetics in genotype 1 chronic hepatitis C patients during therapy with 2 different doses of peginterferon alfa-2b plus ribavirin. Hepatology 2002;35:930-6.