Early changes in hepatitis C virus (HCV) RNA levels predict response to interferon treatment in noncirrhotic HCV patients

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G Fallows, K Kaita, G Minuk, et al. Early changes in hepatitis C virus (HCV) RNA levels predict response to interferon treatment in noncirrhotic HCV patients. Can J Gastroenterol 2000; 14(Suppl B):30B-35B. The role of hepatitis C virus (HCV) RNA quantification in determining ideal interferon (IFN) treatment of noncirrhotic HCV liver disease is uncertain. The specific aim of this study was to determine whether measurement of baseline HCV RNA or changes in HCV RNA levels (HCV RNA) early during therapy predict response to IFN in noncirrhotic HCV patients.

PATIENTS AND METHODS: Twenty-one noncirrhotic patients with chronic HCV were treated with 3 MU IFN -2a three times per week. HCV RNA levels were determined at baseline and after two, four, six, eight and 12 weeks of treatment. Baseline HCV RNA and HCV RNA during therapy were compared with treatment response results at six months. Data were expressed as mean SE, and differences were assessed using Student's *t* test.

RESULTS: Twenty-one patients initiated IFN therapy. Two patients were noncompliant and lost to follow-up. One patient discontinued IFN due to side effects. Apart from age, where responders tended to be younger than nonresponders, the baseline clinical characteristics and alanine aminotransferase (ALT), aspartate aminotransferase, bilirubin and HCV RNA levels did not differ between IFN responders and nonresponders. Levels of HCV RNA were significantly lower after both two and four weeks of therapy in IFN responders compared with nonresponders ($P<0.001$). Changes in log HCV RNA levels after both two and four weeks of therapy were significantly greater in IFN responders compared with nonresponders ($P<0.001$). Changes in log HCV RNA of more than 1.0 after two weeks of IFN therapy identified all six-month responders, with a sensitivity of 100% and a specificity of 89%. Potential financial impact of these findings on patients' management was also calculated. Decisions regarding discontinuation of therapy based on early changes in HCV RNA levels would result in a 40% to 50% reduction in IFN cost.

CONCLUSIONS: In noncirrhotic HCV patients, the change in quantitative HCV RNA after the first two weeks of IFN therapy identifies responders. This finding would result in a 40% to 50% cost savings if decisions about continuing IFN were based on early changes in HCV RNA levels rather than ALT or HCV RNA assessment after the completion of three months of IFN treatment.

Key Words: *Cost analysis; Hepatitis C; Hepatitis C virus; Interferon alpha; Polymerase chain reaction; Quantitative analysis; Therapy*

Des changements précoces dans les niveaux d'ARN du virus de l'hépatite C (VHC) prédisent la réponse au traitement par interféron chez les patients non cirrhotiques atteints d'une hépatite C

CONTEXTE : Le rôle de la quantification de l'ARN du virus de l'hépatite C (VHC) pour déterminer le traitement idéal par interféron (IFN) des patients non cirrhotiques atteints d'une hépatite C est incertain. L'objectif spécifique de la présente étude était de déterminer si des mesures de l'ARN du VHC à la valeur de base ou des changements précoces dans les niveaux d'ARN du VHC (ARN du VHC) pendant le traitement prédisent la réponse à l'IFN chez les patients non cirrhotiques atteints d'une hépatite C.

PATIENTS ET MÉTHODES : Vingt et un patients non cirrhotiques atteints d'une hépatite C chronique ont été traités avec 3 unités souris d'IFN-2 trois fois par semaine. Les niveaux d'ARN du VHC ont été déter-

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Received for publication December 3, 1998. Accepted February 10, 1999

minés à la valeur de référence et après deux, quatre, six, huit et douze semaines de traitement. L'ARN de base du VHC et les changements ( ) dans les niveaux d'ARN du VHC, pendant le traitement, ont été comparés avec les résultats de la réponse au traitement à 6 mois. Les données ont été exprimées comme moyenne ± erreur type, et les différences ont été évaluées à l'aide du test *t* de Student.

RÉSULTATS : Vingt et un patients ont débuté un traitement avec l'IFN . Deux patients n'ont pas observé le traitement et ont été perdus de vue pour le suivi. Un patient a interrompu le traitement à l'IFN à cause d'effets secondaires. Excepté pour l'âge ou les répondeurs tendaient à être plus jeunes que les non-répondeurs, les caractéristiques cliniques de base ainsi que les niveaux d'alanine -aminotransférase (ALT), d'aspartate-aminotransférase, de bilirubine et d'ARN du VHC ne présentaient pas de différence entre répondeurs et non-répondeurs. Les niveaux d'ARN du VHC étaient nettement moins élevés après les deux et les quatre semaines de traitement chez les répondeurs à l'IFN que chez les non-répondeurs (p<0,001). Les changements dans les niveaux logarithmiques de l'ARN du VHC après les deux et les quatre semaines de traitement étaient nettement plus élevés chez les répondeurs à l'IFN que chez les non-répondeurs (p<0,001). Les changements logarithmiques de plus de 1,0 dans l'ARN du VHC après deux semaines de traitement par IFN ont identifié tous les répondeurs à six mois, avec une sensibilité de 100 % et une spécificité de 89 %. L'impact financier potentiel de ces résultats sur la prise en charge des patients a été calculé. Les décisions concernant l'arrêt du traitement et basées sur les changements précoces observés dans les niveaux d'ARN du VHC entraîneraient une réduction de 40 % à 50 % des coûts de l'IFN .

CONCLUSIONS : Chez les patients non cirrhotiques atteints d'une hépatite C, les changements quantitatifs observés dans l'ARN du VHC après les deux premières semaines de traitement à l'IFN identifient les répondeurs. Ce résultat pourrait permettre de réduire de 40 % à 50 % le coût de l'IFN si les décisions concernant le maintien du traitement à l'IFN étaient basées sur les changements précoces des niveaux d'ARN du VHC plutôt que sur l'évaluation des niveaux d'ALT ou d'ARN du VHC à la fin d'un traitement de trois mois avec l'IFN .

Hepatitis C virus (HCV) is an important cause of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC), and is a major indication for liver transplantation (1-5). Elimination of the risk of viral transmission and prevention of the complications related to hepatitis C represent the ultimate goals of therapy. Several studies have suggested that elimination of HCV in individuals with early disease results in decreased severity of liver disease, decreased progression to cirrhosis and decreased risk of HCC (6,7). It should also reduce the need for liver transplantation, improve long term survival and potentially reduce health care costs (8).

Interferon alpha (IFN) is the only therapy currently approved for treatment of chronic HCV (3). IFN requires prolonged administration, with only a small percentage (less than 25%) of those treated having a sustained virological response six months following the end of therapy (4). Given the high cost of IFN (CDN$500/month) and the low rates of sustained viral elimination, selection of patients with the highest likelihood of response to IFN therapy would allow a more appropriate allocation of health care resources.

Several studies have identified clinical and laboratory features that predict response to IFN therapy, but none of these features are sufficiently reliable to be clinically useful in making individual patient decisions (9). Recent studies have shown that baseline HCV RNA quantification may predict response to IFN therapy (10,11). Again the overlap between IFN responders and nonresponders is significant and renders the test clinically less useful in individual cases. A recent study using a quantitative reverse transcription-polymerase chain reaction (RT-PCR) technique suggested that responders to IFN therapy show a decrease in the HCV RNA level as early as two to four weeks into treatment, and that this decrease was predictive of response to IFN (12-14). Confirmation of these findings and their impact on the financial costs of treating chronic HCV patients has yet to be reported.

We, therefore, conducted a prospective study to determine whether quantitative HCV RNA measurement before or early into IFN therapy allows earlier identification of treatment responders and nonresponders than standard biochemical measurements.

PATIENTS AND METHODS

Patient overview: The study was conducted between March 1, 1996 and January 30, 1998 in a large hepatology referral centre and was approved by the ethics and review boards of the University of Manitoba. Patients were considered for inclusion if they were deemed candidates for standard IFN therapy by their attending hepatologist. To be included into the study, patients had to be HCV RNA-positive by qualitative PCR, have abnormal serum alanine aminotransferase (ALT) on two occasions more than four months apart and have liver biopsy evidence of chronic hepatitis with no evidence of cirrhosis (15). Patients were excluded if they had decompensated liver disease, alternative causes of liver disease, clinical autoimmune disease, history of severe depression or suicide attempt, neutrophil count less than 1500 $\times 10^9$/L, platelet count less than 50,000 $\times 10^9$/L, previous IFN therapy or immunosuppression within the past six months, nondermatological malignancy diagnosed in the past five years or active substance abuse within the past six months. Cirrhotic patients were excluded from the study because cirrhosis represents a late stage of the disease. In addition, cirrhotic patients may bias the results in favour of nonresponse to IFN.

Quantitative and qualitative HCV RNA measurements were performed using the Amplicor HCV Monitor test and the Amplicor assay, respectively (Roche Diagnostic Systems, Laval, Quebec). Samples were obtained and processed within 30 mins of venepuncture. After clotting, sera were immediately separated and aliquoted into four to six 2 mL cryovials (to obviate problems with repeat freeze-thaw cycles during subsequent analysis) and then frozen at –70 C until batch tested. Quantitative and qualitative HCV RNA measurements were performed according to kit inserts using primers provided with the kits. Briefly, the quantitative assays were performed as follows. A 100 L serum sample was mixed with 400 L of working lysis buffer containing the

TABLE 1
Comparison of baseline patient characteristics in responders and nonresponders

	Responders (n=9)	Nonresponders (n=9)	P
Age (years)	35.7 7.0	41.9 5.1	<0.05
Sex (% males)	44.4	55.6	0.83
ALT (U/L)	47.3 24	93.3 74	0.08
AST (U/L)	36 18	70 54	0.08
log HCV RNA	4.74 1.07	5.56 0.79	0.09

ALT Alanine aminotransferase; AST Aspartate aminotransferase; HCV Hepatitis C virus

quantitation standard and incubated at 60 C for 10 mins. RNA was precipitated by adding 500 L isopropanol, incubated for 2 mins at room temperature and pelleted by centrifugation at 13,000 *g* for 15 mins. The pellet was resuspended in 1 mL of ethanol before the RNA was repelleted by centrifugation at 13,000 *g* for 5 mins. The pellet was resuspended in 1 mL of specimen dilutent. The synthesis of HCV complementary DNA (cDNA) was achieved by incubating 50 L specimen in specimen dilutent at 60 C for 30 mins. The cDNA was amplified for a total of 35 cycles. PCR products were detected using an enzyme-linked immunosorbent assay test. The number of HCV particles/mL of serum was determined by comparing the optical density values of the specimen and the quantitation standard in a special formula indicated in the kit insert.

Optimal sample size was estimated to be between 20 and 26 patients based on an =0.05 and =0.2 for a power of 0.8, in order to identify a large difference between responders and nonresponders with less than 40% overlap between groups.

Study design: All patients underwent baseline physical examinations and laboratory tests before entering the study. Sera were analyzed for baseline HCV RNA quantification, complete blood counts, liver biochemistry (aspartate aminotransferase [AST], ALT, alkaline phosphatase and bilirubin), albumin and prothrombin time. Patients were treated with IFN -2a (Roferon, Hoffman LaRoche, Nutley, New Jersey) 3 MU subcutaneously three times per week. During therapy, serum was obtained for complete blood count and liver biochemistry at two, four, six, eight, 12, 16, 20 and 24 weeks. Quantitative HCV RNA measurements were assessed in a blinded fashion at two, four, six, eight and 12 weeks. Measurements were not available for the clinicians' review and, therefore, could not be used in patient management decisions. Qualitative HCV RNA measurements were assessed at three and six months.

The focus of this study was to determine the potential utility of HCV RNA assessment in general clinical practice. Therefore, IFN response was based on the recommendations provided by the Canadian Association for Study of the Liver (CASL) Consensus Conference (3). Patients were deemed IFN responders and continued on IFN therapy for 12 months if they normalized their ALT level and became HCV RNA-negative at three months. Patients were deemed nonresponders and IFN was stopped if they had a persistently abnormal ALT level and positive HCV RNA at three months.

Response to IFN was then correlated with, first, baseline clinical and laboratory parameters; second, absolute HCV RNA and ALT levels at specific points into IFN therapy; and, finally, changes in HCV RNA levels (HCV RNA) and ALT (ALT) over the first two and four weeks of IFN therapy. Sensitivity and specificity calculations determined the predictive value of tests, showing a correlation with response to IFN therapy.

Cost of treatment was calculated based on current costs of IFN and its administration (CDN$103/week) and qualitative HCV RNA assays (CDN$50/test) at the authors' institution, along with estimated costs of quantitative HCV RNA assays (CDN$150/test) provided by Roche Diagnostic Systems.

Statistical analysis: Results are expressed as the mean SD. Quantitative data were analyzed by Student's *t* test and ^{2} calculations for determination of statistical significance. P<0.05 was designated as significant.

RESULTS

Twenty-one patients were enrolled into the trial. Two patients required discontinuation of therapy due to noncompliance after two weeks of therapy (lost to follow-up), and one patient required early discontinuation due to side effects (major depression in first eight weeks of therapy, which resolved with medical therapy and discontinuation of IFN). The 18 remaining patients completed at least three months of IFN therapy and were further analyzed.

After three months, nine patients were IFN responders (50%) and nine patients were nonresponders (50%). All patients who were HCV RNA-negative at three months and remained on IFN for 12 months remained HCV RNA-negative. Thus, HCV response at three months predicted 12-month HCV response (true IFN responders).

One patient became HCV-RNA-negative at three months with a decreased (but still mildly elevated) ALT and was kept on IFN by his primary hepatologist. He remained HCV RNA-negative at six and 12 months of IFN therapy, with mild ALT elevation (less than 1.5 times normal) and was considered an IFN responder. This patient remained HCV RNA-negative and clinically well six months after discontinuing IFN, despite persistent mild ALT elevation.

Comparison of the baseline parameters between these groups revealed that responders were younger than nonresponders, but otherwise there was no significant difference in sex, baseline ALT, AST or HCV RNA levels (Table 1). Histological changes assessed using standard measures (15) were not different between responders and nonresponders, but the sample size was too small to have power to demonstrate small differences. Responders to IFN therapy had significantly lower log HCV RNA levels after both two and four weeks of therapy compared with results from nonresponders (P<0.001) (Table 2). Responders to IFN also had significantly lower absolute levels of HCV RNA after two weeks (P<0.001), although the difference after four weeks of ther-

TABLE 2
Absolute hepatitis C virus (HCV) RNA, log HCV RNA, and alanine aminotransferase (ALT) levels in responders and nonresponders at two and four weeks

	Responders (n=9)	Nonresponders (n=9)	P
HCV RNA (10^3 copies/mL)			
2 weeks	3.6 4.5	405 304	0.001
4 weeks	1.8 4.0	416 616	0.06
log HCV RNA			
2 weeks	2.95 0.93	5.16 1.24	<0.001
4 weeks	2.49 0.79	5.03 1.28	<0.001
ALT			
2 weeks	30 17	73 75	0.14
4 weeks	24 10	66 60	0.06

TABLE 3
Changes in hepatitis C virus (ΔHCV) RNA levels, log HCV RNA, and alanine aminotransferase (ALT) in responders and nonresponders early in therapy

	Responders (n=9)	Nonresponders (n=9)	P
HCV RNA (10^3 copies/mL)			
0-2 weeks	205 220	323 400	0.45
0-4 weeks	270 230	313 330	0.44
log HCV RNA			
0-2 weeks	1.79 0.61	0.40 0.48	0.001
0-4 weeks	2.25 0.99	0.52 0.5	0.003
ALT (U/L)			
0-2 weeks	24 20	20 62	0.87
0-4 weeks	26 21	27 56	0.96

apy did not reach statistical significance (P=0.06). ALT levels at two and four weeks did not significantly differ in responders and nonresponders. The rate of decrease in log HCV RNA levels (log HCV RNA) was significantly greater in responders than nonresponders over both the first two and the first four weeks of therapy (P<0.001) (Table 3).

The rate of decrease in absolute HCV RNA levels over the first two and four weeks of therapy did not differ significantly between responders and nonresponders. The rate of change in ALT over the same periods did not differ between the groups. Analysis of other measures of liver function also did not differ significantly between groups (data not shown).

All patients who responded to IFN had a decrease in log HCV RNA of greater than 1.0 or became HCV RNA-negative by quantitative PCR testing after both two and four weeks of therapy (sensitivity 100%). Only one nonresponder had log HCV RNA greater than 1.0 after four weeks, but HCV RNA did not become negative by quantitative testing and levels subsequently increased (specificity 89%). Determination of the log change in viral load was, therefore, able to identify all responders while excluding the majority of nonresponders.

By analyzing these data, four tests were identified that could be used for early recognition of responders to IFN, even in this small group of patients. These included log HCV RNA levels measured at two and four weeks, and log HCV RNA over the first two and four weeks of therapy. The sensitivity of the absolute value of HCV RNA was calculated using log HCV RNA less than 3.0 (1000 copies/mL); this level correlated with both the published lower limit of detection for the assay (approximately 500 to 1000 copies/mL) as well as the mean log HCV RNA values for responders (16,17). Using these criteria, this level of log HCV RNA was associated with low sensitivity after both two and four weeks of therapy (Table 4). Its use as a predictive test would result in the early discontinuation of therapy in patients who otherwise may have responded to therapy. The criterion of a log HCV RNA value greater than 1.0 or a change in HCV RNA status to negative by quantitative PCR testing after two weeks identified all IFN responders, and because log HCV RNA greater than 1.0 is the earliest predictor of response, it may be useful to determine who would benefit from continuation of IFN therapy (Table 4).

TABLE 4
Analysis of predictive tests

	Sensitivity	Specificity
log HCV RNA <3.0		
2 weeks	44%	89%
4 weeks	78%	89%
log HCV RNA >1.0		
2 weeks	100%	89%
4 weeks	100%	89%

Δlog HCV RNA Changes in log hepatitis C virus RNA levels

Cost analysis: A cost analysis was performed to determine the potential savings gained by early discontinuation of therapy (proposed model) versus standard therapy (standard model). The proposed model costs are based on continuing IFN beyond two weeks only for patients who had log HCV RNA greater than 1.0 or who had undetectable HCV RNA levels at two weeks. The standard model costs are based on continuing IFN after 12 weeks only if the patient's ALT level normalizes. Based on the authors' data, the number of patients defined as responders at 12 weeks is the same in both models, regardless of the response rate, because all 'ALT responders' will be 'HCV RNA responders'. All of these patients will continue on IFN. Therefore, the cost savings will be realized only through early recognition of nonresponders in the proposed model, who would have been continued for a full 12 weeks on IFN in the standard model. This number will vary with IFN response rates, variably reported in the literature from 30% to 50%. The lower the response rate to IFN (IFN continued for 12 weeks in more nonresponders), the greater the cost advantage of early recognition of nonresponders (Tables 5 and 6).

Cost was calculated in terms of IFN cost alone and total

TABLE 5
Potential cost savings in first 12 weeks therapy (interferon [IFN] alpha cost alone)

RR	IFN cost/100 patients – standard therapy model	IFN cost/100 patients – proposed model	IFN cost savings/100 patients	% cost savings
50%	$123,600	$77,250	$46,350	38%
40%	$123,600	$67,980	$55,620	45%
30%	$123,600	$58,710	$64,890	53%

All costs are in Canadian dollars. RR Response rate

cost of therapy (IFN plus estimated HCV testing costs). It was found that discontinuation of IFN after two weeks of therapy in patients not fulfilling the criteria would lead to a 38% to 53% reduction in the cost of IFN alone, depending on the response rate to IFN (Table 5). An estimate of the overall cost savings was then calculated, which incorporated the cost of HCV RNA testing – quantitative HCV RNA testing at study start and at two weeks in the proposed model, and qualitative HCV RNA testing at study start and at 12 weeks in the standard therapy model. Early discontinuation of IFN in nonresponders would lead to a combined reduction in costs of at least 18% to 32% (Table 6).

TABLE 6
Potential combined cost savings in the first 12 weeks (interferon [IFN] alpha cost and hepatitis C virus [HCV] RNA testing)

RR	HCV testing cost	Combined cost/100 patients	Combined cost savings/100 patients	% combined cost savings
Proposed therapy model				
50%	$30,000	$107,250	$23,850	18%
40%	$30,000	$97,980	$32,620	25%
30%	$30,000	$88,710	$41,390	32%
Standard therapy model				
50%	$7,500	$131,100		
40%	$7,000	$130,600		
30%	$6,500	$130,100		

All costs are in Canadian dollars. RR Response rate

DISCUSSION

HCV is an important cause of chronic liver disease and HCC (4,5). Of those infected with the virus, 70% to 90% develop chronic HCV infection (5,18). Using normalization of ALT at six months as an endpoint for treatment, IFN results in a 40% to 60% biochemical response rate. However, over the subsequent 18 months, 50% to 75% of responders have a biochemical relapse (6,19). Many of these patients remain HCV RNA-positive despite normalization of the ALT level, and these patients have a high frequency of relapse. Thus, ALT measurement may not be sensitive enough to separate responders from nonresponders clearly. Virological response to IFN (negative qualitative HCV RNA assay) ranges from 25% to 50% after six months of therapy (1). Longer duration of therapy (12 months) increases response rate slightly and decreases the frequency of relapse (20). Long term sustained viral response to IFN therapy alone remains low (less than 25%) (4,20-23).

Management decisions concerning HCV are difficult due to the poor efficacy of available therapy, the high cost of therapy and the inability to predict which patients will respond to therapy (3,4). Pretreatment features that are associated with a greater likelihood of response to IFN include young age, shorter duration of infection, low levels of HCV RNA, viral genotypes 2 or 3 and the absence of fibrosis or cirrhosis on liver biopsy (1,9,10,24-27). Previous analysis of our HCV population has shown that the HCV genotype 1 predominated (64%), with roughly equal numbers of 1a and 1b (Rosser, unpublished data). In our study, genotype analysis was not determined because identification of differences between responders and nonresponders would have been unlikely in this small group.

More recently, RT-PCR quantification of HCV RNA has shown that responders to IFN have decreases in HCV RNA as early as two to four weeks into therapy (12-14,28). If this is true in the general population, HCV RNA quantification could replace ALT assessment for prediction of response to therapy. Unfortunately, only limited information is available regarding the performance characteristics of this assay. Published data state that it is capable of measuring HCV viral load as low as 500 to 1000 RNA copies/mL, although it is associated with high assay variability (16). Replicate testing of the same sample in the assay yielded a standard deviation of ±0.311 log (17).

Lee and co-investigators (23) have shown that sustained viral responders had the most rapid decrease in HCV RNA, reaching undetectable levels in some patients by week 2. Patients who responded but ultimately relapsed had delayed clearance of HCV RNA from serum. However, this study did not look at the change in HCV RNA from baseline as a predictive factor, and over 50% of eventual responders were not identified at two weeks. This finding is similar to our results, wherein HCV RNA negativity by our assay at two weeks identified only 44% of responders. This is unacceptable in clinical decision-making.

In an attempt to find more reliable predictors of response to IFN therapy, we analyzed the changes in HCV RNA levels early in the course of therapy. We found that at our centre becoming HCV RNA-negative by quantitative PCR assay or decreasing the log HCV RNA to greater than 1.0 over the first two weeks of therapy with IFN identified responders with a sensitivity of 100% and specificity of 89%. By using this test to predict response, we found that it could lead to a reduction of 38% to 52% in the cost of IFN alone, and at least an 18% to 28% reduction in the total cost based on a present estimation of the cost of quantitative HCV RNA testing.

The cost of the quantitative HCV RNA assay is high (about CDN$150/sample) because it is new test and not done routinely in HCV management. Greater acceptance of

this test and subsequent greater use would lead to lowering of the cost per test and significant cost savings.

Gavier et al (14) found that failure to clear HCV RNA after one month of therapy was associated with a very low probability of sustained response to IFN. In our study, one of nine patients (11%) remained viremic after four weeks of therapy, but the level subsequently became undetectable at eight weeks. A significant number of patients with viral persistence at two weeks actually responded to therapy (five of nine patients [56%]). An undetectable quantitative HCV RNA level alone (ie, fewer than 500 copies/mL) was a poor predictor of response to therapy in our study, with a sensitivity of 44% after two weeks and 78% after four weeks of therapy. A stronger correlation was found by using this criterion in conjunction with the change in viral load early into therapy.

It is also not surprising that absolute changes in HCV RNA levels did not predict response. A change from 1,000,000 copies/mL to 500,000 copies/mL is a similar numeric change as from 500,000 copies/mL to 1 copy/mL but clearly represents a different biological response. The log HCV RNA (0.3 versus 5.7 in the previous example) is a much better biological measure of viral response.

Recent studies suggest that the combination of IFN and ribavirin lead to better response rates and prolonged viral eradication compared with IFN therapy alone (22). It is not clear that response to combination therapy parallels early changes in viral load and, as such, the criteria used for discontinuing therapy in our proposed model should not be used in this group. Further studies in patients treated with combination therapy will determine whether the criteria we defined can be extended to this therapy. However, some patients are unable to take combination therapy (eg, due to hematological side effects), and in this population, our criteria should be helpful in optimizing IFN therapy.

CONCLUSIONS

This study provides preliminary evidence that quantitative HCV RNA may be used as a marker of early clinical response to IFN therapy. Discontinuation of therapy based on quantitative changes in HCV RNA will lead to significant cost savings and a decrease in the unnecessary side effects of prolonged therapy in patients unlikely to respond to IFN treatment.

ACKNOWLEDGEMENTS: This work was supported by grants from Manitoba Medical Services Foundation (Dr Barry Rosser) and Hoffman-LaRoche Pharmaceuticals.

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