CLINICAL STUDIES

Chronic Hepatitis C: Treatment Comparison Between 3 and 5 Million Units of Interferon Alpha-2b

FERNANDO CASTRO, MD; ESTHER A. TORRES, MD; JUAN OHARRIZ, MD;
CARMEN GONZÁLEZ-KEELAN, MD*; CYNTHIA PÉREZ, PhD†; CARLOS RUBIO, MD‡

ABSTRACT. Interferon (IFN) is the only drug that has been approved by the FDA for therapy of chronic hepatitis C. However, optimal dose and duration of therapy are still controversial. This study compares the effectiveness of treatment of chronic hepatitis C patients with 3 vs. 5 million units (MU) of recombinant alpha-interferon 2-b three times per week. We also evaluated the relapse rate with a shorter 12 week-course of therapy in those patients who had normalizaton of aminotransferases by week 12. Seventy-five patients were randomized to receive either 3 vs. 5 MU of IFN; seventy-two completed the study. A complete response was seen in 11/35 (31%) of those treated with 5 MU vs. 13/37 (35%) in the 3 MU dose (p=0.74). Patients were followed after IFN was withdrawn and only 2 had persistently normal aminotransferases. Analysis of multiple variables was done to predict response to IFN and only elevations of GGT, ferritin and alkaline phosphatase were found to be predictors of a poor response. Therefore, we recommend initial therapy with 3 MU of IFN for a longer period than 12 weeks in patients who show a response. *Key words: Hepatitis C, Interferon*

The hepatitis C virus (HCV) is a significant cause of chronic morbidity and mortality. It is currently the most common cause of chronic liver disease in the United States along with alcoholism (1). About 80% of those who are infected with HCV go on to develop chronic infection, and 20 to 40% of these will eventually develop cirrhosis, usually over a 20 year span (2, 3).

Interferon (IFN) is the only drug that has been approved by the Food and Drug Administration for therapy of chronic HCV infection. Treatment with IFN is associated with a low response rate, significant side effects, and its cost effectiveness is uncertain. Studies on IFN cost-effectiveness have not been done prospectively. Instead, computer models that simulate patient outcome have been utilized. These studies have suggested that a 6-12 month course of IFN is cost effective as compared with other accepted medical therapies (4,5). If we define initial response rate as the normalization of aminotransferase levels at the time IFN is discontinued, therapy with the recommended dose of 3 million units (MU) three times per week for 24 weeks is associated with a 40% initial response (6-9). Relapse, defined as elevation of aminotransferases above the normal range after discontinuing IFN, occurs in 50 to 90% of patients within six months after interferon therapy is withdrawn. Therefore, only about 15% of patients treated with IFN for 6 months show a sustained response (6-9).

A number of studies have suggested that a longer treatment course of IFN for 12 to 24 (10) months is associated with a higher percentage of sustained response reaching a range of 20-30%. However, IFN is associated with side effects that can cause premature withdrawal of therapy in 10-15% of patients (11). Studies have not addressed whether a shorter 3 month course of IFN in patients who show a rapid normalization of aminotransferase values is associated with a sustained response rate similar to that seen with a 6 month course of therapy.

Although the recommended dose of IFN for chronic HCV infection is 3 MU, higher doses are used for hepatitis B infection and other diseases. Controversy exists as to whether a higher dose of IFN will achieve a higher initial or sustained response rate.

The purpose of our study was to compare the efficacy of treatment of patients with chronic hepatitis C with 3 vs. 5 MU of recombinant alpha interferon 2-b (Intron A,

From the Department of Medicine, Gastroenterology Section; the *Department of Pathology and the †Graduate School of Public Health, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico.

‡ Deceased.

Address for correspondence: Esther A. Torres MD, Department of Medicine, University of Puerto Rico Medical School, PO Box 365067, San Juan, PR, 00936-0350

This study was sponsored in part by a grant from Schering-Plough Caribbean.

Schering-Plough, Kenilworth, NJ) three times per week. We compared the response and relapse rates between the two groups. Furthermore, we also wanted to evaluate the possibility of reducing costs of therapy and obtain data on the relapse rate with a shorter 12 week treatment course. Therefore, we compared the relapse rate of a twelve week treatment in those patients who had shown a complete response vs. continued treatment for 24 weeks in patients who had a significant decrease although not a complete normalization in ALT.

Methods

From September 1991 to February 1995, we studied 75 patients with chronic hepatitis C referred to the Gastroenterology Research Unit for evaluation. Chronic hepatitis C was defined as follows: an elevated serum alanine aminotransferase (ALT) level of 2.5 times the upper limits of normal or greater on two or more occasions for at least six months, a positive hepatitis C antibody by RIBA II, and a histological diagnosis of chronic active hepatitis with or without cirrhosis.

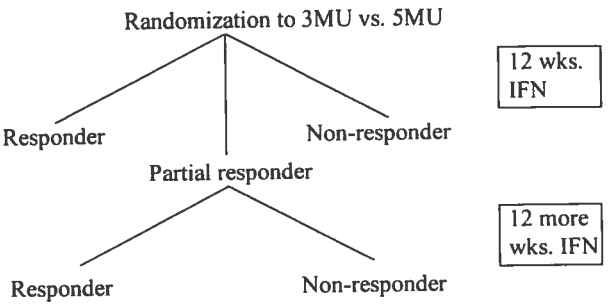
Exclusion criteria included previous interferon therapy, other antiviral therapy in the previous six months, chronic ethanol consumption of 60 gms/day or more, hemophilia, positive HIV, pregnancy, serious medical illness other than liver disease that could prevent completing the study, significant hepatic failure characterized by hepatic encephalopathy, bleeding esophageal varices, intractable ascites, serum bilirubin levels above 4 mg/dl, serum albumin less that 2.5 gm/dl, prothrombin time more than 4 seconds over control, cytopenia characterized by a platelet count below 100,000 per mm3, a leucocyte count below 3,000 per mm3, granulocytes below 1,500 or an hemoglobin concentration below 11 gm/dl, and a serum creatinine over 2.5 mg/dl.

Other causes of liver disease were excluded by history, serologic testing (ceruloplasmin, ferritin, antinuclear antibodies, antismoothmuscle antibodies, antimitochondrial antibodies, hepatitis B surface antigen, alpha-1 antitrypsin) and liver biopsy.

After the initial evaluation, patients were randomly assigned to receive either 3 or 5 MU of IFN by subcutaneous injection three times per week for 12 weeks. All patients were seen in our clinic at 1, 2 and 4 weeks after starting therapy and then monthly for the duration of the treatment. Complete blood count and blood chemistries were done at each follow-up visit and patients were monitored for compliance and side effects.

After 12 weeks of interferon treatment, the patients were assessed for response and classified as complete, partial or non responders based on ALT levels. Complete response was defined as normalization of serum aminotransferase levels. Partial response was defined as a decrease in ALT levels of more than half of baseline or a total value of less than 2 times the upper limit of the normal range. No response was defined as no significant change or further elevation of baseline ALT. (Fig. 1). All complete responders discontinued treatment after 12 weeks and were followed for an additional 12 months at 2 month intervals to assess relapse or sustained response. Relapse was defined as any abnormality in ALT above the upper limit of normal and sustained response as persistently normal ALT. Therapy was discontinued after 12 weeks in all non responders. Partial responders continued treatment at the same dose for an additional 12 weeks for a total of 24 weeks of r-IFN. After ending 24

Figure 1. Interferon Treatment Scheme



Responder = Normal aminotransferases
Partial responder = Decrease ALT by 50% or ALT<2x ULN
All responders were followed for 12 months after therapy d/c to assess relapse

weeks of therapy, patients were reassessed and reclassified as complete responders or non responders (defined at this point as any abnormality of ALT). Therapy could be discontinued at any time because of serious adverse experiences, voluntary patient withdrawal, failure of compliance or a decision by the investigators that this would be in the patient's best interest.

The patients were instructed on self-administration of the drug and treatment was done at home. This study was approved by the Institutional Review Board of the Medical Sciences Campus and written consent was obtained from all patients. Means were compared using the Student's t test. Proportions were compared using the chi-square test or Fisher's exact test when appropriate. Logistic regression was used to evaluate the association between response to interferon and study variables (predictors). All p values are two sided.

Results

Seventy-two of the original seventy-five patients completed the study. Two patients randomized to 5 MU withdrew from the study; one of these patients started using intravenous drugs and another was lost to follow up after 8 weeks of therapy. One patient in the 3 MU arm was actively using alcohol and discontinued IFN administration. Of the seventy-two who completed the study, thirty-five patients were assigned to receive 5 MU and thirty-seven to receive 3 MU of IFN.

The 3 MU and 5 MU dose groups were similar with respect to age, sex, symptoms, physical findings, liver function tests, risk factors for disease acquisition, years since first known ALT rise, years since probable exposure, liver histology and Knodell's histology activity index. (Table 1). Twelve patients (17%) had chronic persistent hepatitis on liver biopsy, thirty-eight (53%) had evidence of chronic active hepatitis, and cirrhosis was found in 22 (30%).

After twelve weeks of therapy, complete normalization of ALT was present in 19/72 patients (26%), whereas 27/72 (38%) were classified as non-responders. All of these patients discontinued therapy with IFN at this point as per protocol. Six of the non-responder patients, three in each arm, had been initially classified as partial responders but refused further IFN therapy and were reclassified as non-responders. Another patient receiving 5 MU of IFN developed urticaria so therapy was discontinued in week 11. She had abnormal aminotransferases and was also classified as a non-responder. After 12 weeks of therapy, the 37 patients randomized to receive 3 MU of IFN were classified as follows: 11/37 (29.7%) were responders, 10/37 (27%) partial responders, and 16/37 (43.3%) were non-responders. Among those patients receiving 5 MU, 8/35 (22.9%) were classified as responders, 16/35 (45.7%) were classified as partial responders, and 11/35 (31.4 %) as non responders. (Fig. 2). Twenty-six patients were classified as partial responders in week twelve and continued receiving IFN for a total of 24 weeks. Sixteen of these 26 patients had been randomized to 5 MU of IFN and 10 patients received 3 MU. In the 5 MU arm of the study, 3/16 (19%) were finally classified as responders after completing the 24 weeks and 13/16 (81%) as non responders. Among those patients randomized to receive 3 MU and initially classified as partial responders by week

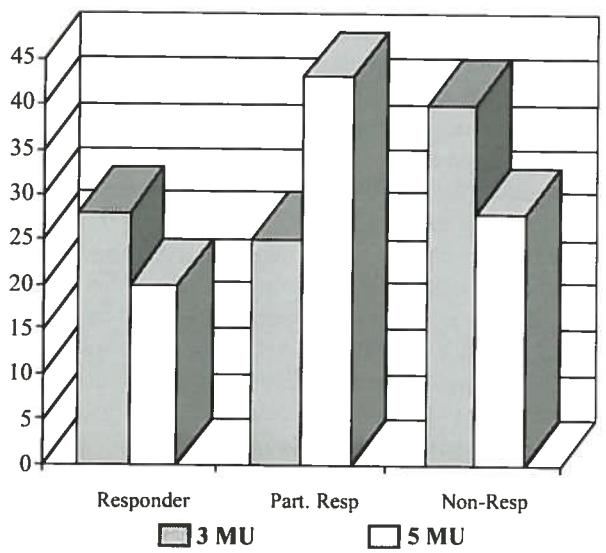


Figure 2. Results after 12 weeks of therapy

Table 1. Baseline characteristics of the 3MU and 5MU dose groups.

	3MU	%MU	pVALUE
Age	43.6±1.4	46.4±2.1	0.26
Gender: M/F	50% male	59% male	0.41
Risk factors*	87% any present	76% any present	0.41
Symptoms†	63%	62%	1.0
Physical findings‡	18.4%	27%	0.42
Duration ABN.	38.2±9.6 months	27.8±4.3 months	0.33
LFT's			
Duration risk	17.4±1.6 years	18.7±2.1 years	0.06
Factors			
AST	138±10	123±10	0.31
ALT	193±12	186±16	0.74
GGT	100±10	102±12	0.91
AP	115±7	125±8	0.33
Albumin	4.55±0.06	4.59±0.06	0.71
Ferritin	242±58	263±31	0.76
SIBC	289±20	296±16	0.80
Liver			1.0
Histology**			
Knodell's score	10.1±0.8	10.6±0.8	0.65
Fibrosis	1.82±0.3	1.97±0.3	0.71
Inflammation	3.14±0.17	3.20±0.16	0.82

* Risk factors assessed were: blood transfusion, intravenous drug use, high risk sexual behavior, homosexual contact, needlestick expusure.
† Symptoms: general malaise, weight loss, fever, anorexia, abdominal discomfort, jaundice, acholia, choluria
‡ Physical finding: jaundice, gynecomastia, spider angioma, ascites, RUQ tenderness, palmar erythema, hepatomegaly, splenomegaly, peripheral edema, collateral circulation
** Liver histology: chronic persistent hepatitis, chronic active hepatitis,cirrhosis

12, 2/10 (20%) had an end of treatment response vs. 8/10 (80%) classified as non responders.

At completion of therapy, the complete response was 31% (11/35) among those patients treated with 5 MU of IFN as compared to 35% (13/37) in those who received 3 MU. (p = 0.74). (Fig. 3). Patients were followed for 12 months after concluding therapy with IFN. A sustained response, defined as persistently normal ALT levels, occurred in only two patients. Both of these had received 3 MU, one patient for a 12 week period and the other for 24 weeks. (p = 0.49).

The majority of patients had side effects common with IFN use, such as flu-like illness and fatigue. These were of minor consequence and did not require dose reduction.

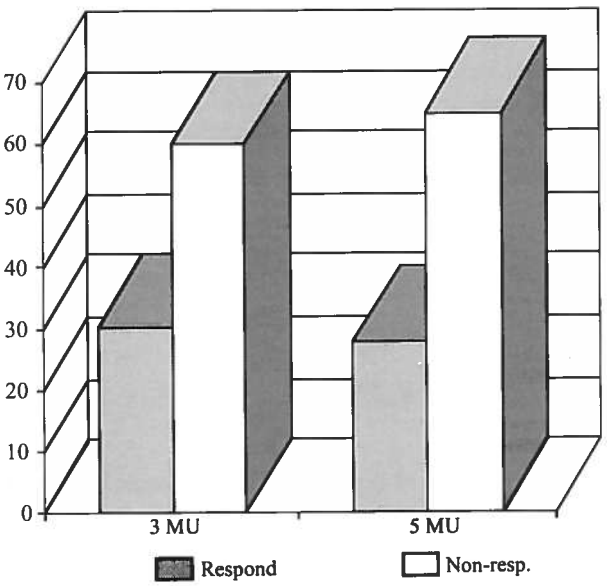


Figure 3. Response after completing therapy.

However, two patients randomized to the 5 MU dose required dose reduction or discontinuation due to serious side effects. One patient developed urticaria and IFN was withdrawn at week eleven and another had thrombocytopenia of 15,000 in the fourth week. She had no evidence of bleeding but required admission to the hospital and transfusion of 10 units of platelets. In this last patient IFN therapy was interrupted for a 2 week period until platelets returned to normal. The dose was subsequently reduced to 3 MU and was well tolerated although she did not normalize aminotransferases..

A number of clinical, histological and laboratory variables were evaluated to try to predict response to IFN therapy. Elevations of GGT, ferritin and alkaline phosphatase were found to be predictors of a poor response (p = 0.0001, 0.03 and 0.03 respectively). (Table 2). Although only 23% of patients with cirrhosis were classified as responders vs. 34% of those who showed chronic active hepatitis on liver biopsy and 50% of those with chronic persistent hepatitis, these results were not statistically significant. Thus, liver histology was not a predictor of response to IFN in our study group.

Table 2. Clinical Characteristics According to Response to Interferon

Characteristic	Responder (N=24)	Non-responder (N=48)	P value
Age	43.5±2.2	46.3±1.6	0.31
AST	113.5±11.2	140.6±9.3	0.08
ALT	197.3±20.1	187.7±11.7	0.66
Knodell score	9.5±0.9	10.7±0.7	0.34
GGT	58.±6.6	121.3±10.5	0.0001
Albumin	4.6±0.1	4.6±0.1	0.71
AP	103.7±6.9	127.3±6.8	0.03
SIBC	264.9±22.4	314.2±13.9	0.06
Duration since exposure	17.0±1.7 years	18.5±1.8 years	0.57
Fibrosis	1.5±0.3	2.1±0.2	0.16
Inflammation	3.4±0.2	3.1±0.2	0.24
Ferritin	168±19	287±49	0.03

Discussion

A number of studies have attempted to improve the 40% initial response rate of chronic hepatitis C patients with IFN by increasing the starting dose from 3 MU to 5 MU with conflicting results. However, the majority of these studies have not shown a significant improvement with the higher dose (7,12-14).

Starting therapy with 5 MU of IFN would not only add costs but may result in more frequent serious side effects (11,15) such as leukopenia and thrombocytopenia, flu-like symptoms, irritability and depression. The two patients in our study who developed serious side effects received 5 MU of IFN. Some consideration can be given to increasing the dose from 3 MU to 5 MU in selected patients after no response is observed at week twelve of treatment. Lindsay et al. conducted a trial in which patients that did not respond to an initial dose of 3 MU were increased to 5 MU by week 12. An additional 10% exhibited normalization of aminotransferases at the end of treatment (7). However, none of these patients had a sustained response at week 24 of follow-up.

IFN is associated with significant side effects that can result in decreased productivity and loss of workdays (16). It is also an expensive drug, with an average cost of $3,700 per patient for a 6-month-course of 3 MU three times per

week. If therapy for 3 months could offer similar response rates to a 6-month course it could represent an option for certain patient groups who could not afford further therapy or developed significant side effects. Only 2 patients out of the 72 who completed therapy in our study group exhibited a sustained response after 12 months of observation (2.8%). This is markedly below the 15% sustained response rate reported in the literature after 6 months of treatment. Therefore, we do not recommend stopping treatment after 12 weeks in those patients who show an initial response.

Substantial differences have been reported in the treatment response to IFN between different patient populations (17,18). Our overall response rate of 33% is slightly lower than the 40% reported among studies in the United States. A number of factors related both to the patient population as well as the hepatitis C virus can account for these differences. At least 6 genotypes of hepatitis C have been identified (19), and genotype I has been associated with a poor response to therapy (20-21). We have found a predominance of genotype I in Puerto Rico (22).

High viral titers have also been related to a poor response to therapy. Neither the genotype nor the viral titers were determined in this study. Among the host characteristics that have been associated with a poor response is cirrhosis (21) which was present in 30% of our population. This high rate of cirrhosis could partially explain the slightly lower response rate.

After analysis of multiple variables, elevated GGT was found to be the most reliable marker of a poor response. Although this enzyme can sometimes be elevated without evidence of liver disease, it has been found by others to correlate with a poor response (23). No difference in the therapeutic response between the 3 MU and 5 MU dose of IFN was found. Considering the higher costs and the incidence of more severe side effects, we recommend an initial 3 MU dose. A 12 week course of treatment was associated with a higher relapse rate, thus a longer period of therapy is advisable.

References

1. Alter MJ. The epidemiology of acute and chronic hepatitis C. Clinics in Liver Disease 1997; 1: 559-568.
2. Di Bisceglie A, Goodman ZD, Ishak KG, et al. Long-term clinical and histologic follow up of chronic post transfusion hepatitis. Gastroenterology 1991; 14: 969-974.
3. Alter MJ, The detection, transmission and outcome of hepatitis C virus infection. Infect Agents Dis 1993; 2: 55-66.
4. Younossi ZM, McHutchison JG. Interferon treatment of chronic HCV infection: an economic analysis of different strategies (abstract). Gastroenterology 1996; 110:A47
5. Kim WR, Poterucha JJ, Gross JB, et al. Cost effectiveness of 12 month of interferon-alfa treatment for chronic hepatitis C (abstract). Gastroenterology 1996; 110: A1233.
6. Davis GH, Balart, LA., Schiff, ER., et al. Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter randomized, controlled trial. N Engl J Med 1989; 321: 1501-6.
7. Lindsay KL, Davis GL, Schiff ER, et al. Response to higher doses of interferon alfa-2b in patients with chronic hepatitis C: a randomized multicenter trial. Hepatology 1996;24:1034-40.
8. Marcellin P, Boyer N,Giostra E, et al. Recombinant human alpha-interferon in patients with chronic non-A, non-B hepatitis: a multicenter randomized controlled trial from France. Hepatology 1991;13:601-3.
9. Causse X, Godinot H, Chevallier M, et al. Comparison of 1 or 3 MU of interferon alfa-2b and placebo in patients with chronic non-A, non-B hepatitis. Gastroenterology 1991;101:497-502.
10. Poynard T, Lergy V, Cohard M, et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 1996;24:778-89.
11. Okanoue T, Sakamoto S, Itoh Y, et al. Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol 1996;25:283-91.
12. Benelux multicentre trial of alpha interferon treatment for chronic hepatitis C: standard vs. high dose treatment monitored by biochemical and virological markers (interim analysis) Gut 1993; 34 (2 suppl): S 119-20.
13. Marcellin P, Pouteau M, Boyer N, et al. Absence of efficacy of an increasing dosage schedule on the response rate during and after recombinant alpha interferon therapy in chronic hepatitis C. Hepatology 1991;14:71 (abstract).
14. Bellary S, Smith D, Bankes P, et al. High dose interferon alpha-2b therapy for chronic hepatitis C: an open study of the response and predictors of response. Am J Gastroenterol 1995; 90: 259-262.
15. Bonkousky HL, Clifford BD, Smith LJ, et al. High-dose interferon alfa-2b for re-treatment of non-responders or relapsing patients with chronic hepatitis C, a controlled randomized trial. Dig Dis Sci 1996;41:149-154.
16. Fattovich G, Giusting G, Favarato S,et al. A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol 1996;24:38-47.
17. Diodati G, Bonetti P, Noventa F, et al. Treatment of chronic hepatitis C with recombinant human interferon - alpha 2a; results of a randomized controlled clinical trial. Hepatology 1994;19:1-5.
18. Tine F, Magrin S, Craxi A, et al: Interferon for non-A, non-B chronic hepatitis: A meta-analysis of randomized clinical trials. J Hepatol 1991;13:192-96.
19. Simmonds P, Alberti A, Alter HJ, et al: A proposed system for the nomenclature of hepatitis C viral genotypes (letter). Hepatology 1994;19:1321-1324.
20. Martinot-Peignoux M, Marcellin P, Pouteau M, et al. Pretreatment serum hepatitis C virus RNA levels and hepatitis C virus genotypes are the main and independent prognostic factors of sustained response to interferon alpha therapy in chronic hepatitis C. Hepatology 1995;22:1050-6.
21. Davis GL. Prediction of response to interferon treatment of chronic hepatitis C. J Hepatol 1994;20:1-3.
22. Rodríguez-Medina JR, Pérez W, Gallagher J, Martin J, Castro F, Torres E. Hepatitis C virus genotype prevalence and interferon treatment outcomes in Puerto Rican patients (Abstract) P R Health Sci J 1997;16:228.
23. Brillanti S, DiFebo G, Ricci P, et al. Statistical analysis of factors predicting response to alpha interferon therapy in 108 adult patients with chronic community-acquired hepatitis C. Gastroenterology 1993;104:A880.