Response to Combination Therapy of Interferon Alfa-2b plus Ribavirin in Hispanics with Chronic Hepatitis C

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Objective. **To evaluate the response rate of Hispanics with chronic hepatitis C to combination therapy of interferon alfa-2b plus ribavirin and to assess its adverse events.**

Background. **Hepatitis C virus may lead to chronic infection and multiple complications. Response to combination therapy of interferon plus ribavirin has been studied in many populations. African Americans have been found to have a lower response rate than Caucasians. However, little data exist for Hispanics.**

Methods. **Hispanic patients from Puerto Rico with chronic hepatitis C were eligible for the study between November 1997 and February 2000. The Institutional Review Boards of the participating institutions approved the study. Written informed consents were obtained. Combination therapy was given for 48 weeks and patients were followed for 24 weeks after treatment. Analysis of response to therapy was performed in an intention-to-treat basis.**

Results. **The most frequent adverse event was anemia (89%), associated to ribavirin. Sustained response was 23% for naive patients, 45% for relapsers, and 8% for non-responders to previous interferon monotherapy ($p < 0.001$). Data to analyze response was not available in 27% of patients. Hispanic patients had a low response rate to combination therapy.**

Conclusions. **Response rates to combination therapy for Hispanic naive and previously non-responder patients are lower than in other reported populations. This may be due to a high prevalence of genotype 1 in Puerto Rico, which is associated to poor response. The higher response rate of relapsers, similar to those reported previously, was expected since these patients showed a previous response to interferon monotherapy. Ethnic factors may play a role in the response to therapy and should be further studied to determine proper treatment strategies for this population.**

Key words: Interferon, Ribavirin, Hispanic, Hepatitis C, Puerto Rico, Ethnicity, SVR, Genotype 1.

Hepatitis C virus (HCV) is a ribonucleic acid (RNA) virus and a member of the Flaviviridae family. Six different genotypes have been identified based on nucleotide sequence heterogeneity (1). HCV has infected approximately 170 million persons worldwide and the prevalence of antibodies to HCV had been found to be 1.8% in the United States (US) general population (2). However, an elevated prevalence of HCV infection was found among adults aged 21-64 years old residing in the municipality of San Juan, Puerto Rico (3). Approximately 75% of those infected will develop chronic infection (4) (presence of virus RNA in the blood for at least six months) (5). The infection may progress to cirrhosis in up to 25%, complicated by ascites, encephalopathy, variceal bleeding, and hepatocellular carcinoma (1% to 4%). Extrahepatic manifestations include mixed cryoglobulinemia, porphyria cutanea tarda, and lichen planus, among others. Infection is primarily by percutaneous exposure with approximately 65% of patients having a history of intravenous drug use and 15% having received blood transfusions before 1990, when blood began to be screened for HCV. Other causes of infection are needle stick injuries, intranasal drug use, sexual transmission, and vertical transmission (4).

Treatment of chronic hepatitis C has consisted of monotherapy with an interferon alfa or combination therapy of an interferon alfa plus ribavirin. Interferon works by binding to specific receptors on the cell surface that initiate

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a cascade of protein-protein interactions leading to rapid activation of gene transcription. It may result in the inhibition of viral replication in infected cells, inhibition of cell proliferation, and immunomodulation. Ribavirin is a nucleoside analog with antiviral activity against RNA and deoxyribonucleic acid (DNA) viruses (6). The most common adverse events of combination therapy of interferon alfa-2b plus ribavirin are fever (56%), fatigue (55%), headache (52%), and myalgia (50%). Nausea (33%), depression (30%), anorexia (22%), and dermatitis (18%) may also occur (7). Anemia occurs in 25 to 36% (8), attributable to hemolysis caused by ribavirin (9). Pegylated interferons were later introduced and HCV therapy shifted to the pegylated formulations used alone or in combination with ribavirin (6). Pegylation is the attachment of an inert and water-soluble polyethylene glycol polymer to the interferon, which increases the duration of biologic activity and may reduce the immunogenicity of interferon (6, 10). The best indicator of effective treatment is a sustained virologic response (SVR). SVR is defined by the absence of detectable HCV RNA in the serum as shown by a qualitative HCV RNA assay with lower limit of detection of 50 IU/mL or less at 24 weeks after the end of treatment (5).

There is controversy about the role of ethnicity in predicting treatment response on hepatitis C. A higher prevalence of HCV infection has been found in African Americans (2) and also an increased incidence of hepatocellular carcinoma (11). Treatment studies have shown a lower response rate in African Americans than in whites. Studies with consensus interferon alfa-2b have shown a significantly lower response to treatment among African Americans as compared to Caucasians (2% vs. 12%) (12). This difference had been attributed to a higher prevalence of HCV genotype 1 in the African American population as compared to Caucasians. HCV genotype 1 has been associated with a lower rate of response to treatment than other genotypes (5). When adjusted for genotype, response is still significantly lower at the end of treatment in African Americans as compared to Caucasians, but sustained response is not significantly different (3% vs. 7%). Differences in response rates were also seen on a trial with combination therapy of interferon plus ribavirin for African Americans compared to Caucasians but no difference was observed when adjusted for genotype (13). When naive African Americans are treated with combination therapy that currently includes pegylated interferon alfa, they have a SVR ranging from 25% for pegylated interferon alfa-2b (14) to 26% for pegylated interferon alfa-2a (15); this SVR is higher than for non-pegylated interferon but still lower than SVR for Caucasians (39%) (15).

There is limited data on treatment response in Hispanic populations, as studies have included small number of patients. Studies with consensus interferon showed no difference on sustained response or genotype distribution in Hispanics as compared to Caucasians (12). Studies with combination therapy of interferon plus ribavirin have shown an increased prevalence of genotype 1 in Hispanics, but less than in African Americans. The lower SVR (8%) to interferon in Hispanics seemed to improve with the addition of ribavirin in a 48-week combination therapy for naive patients, but in view of the small number of patients, adequate conclusions could not be reached (13).

We report the results of a clinical trial that evaluated the response rate of Hispanics with chronic hepatitis C to combination therapy with interferon alfa-2b plus ribavirin and its adverse events in two major medical centers in San Juan, Puerto Rico. This study included a higher number of Hispanic patients than that of previous studies, allowing for historical comparison of our response rate with that of other races.

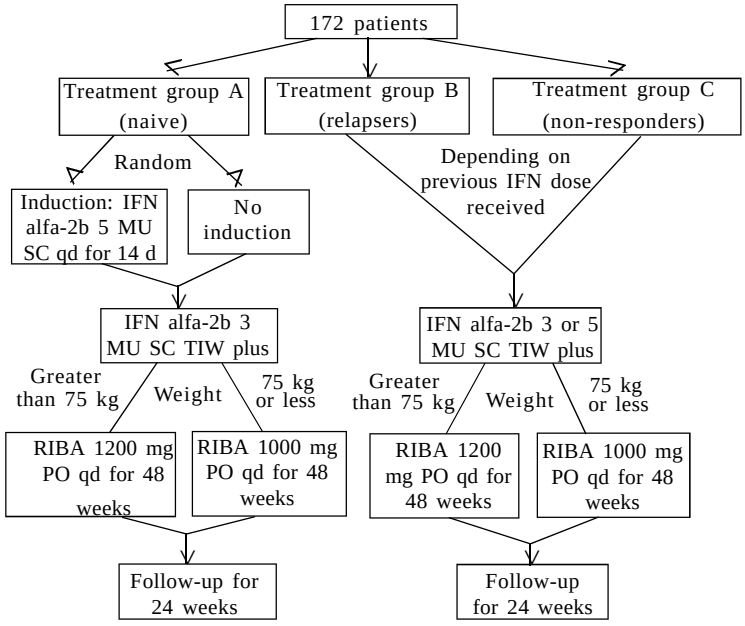
Methods

Design. This study evaluated the response rate to treatment with interferon alfa-2b plus ribavirin in naive patients with chronic hepatitis C and relapsers and non-responders to prior treatment with interferon alfa. Naive patients were participating in a Latin American multicenter randomized, controlled clinical trial designed to compare early response rate between two treatment schemes with interferon alpha-2b plus ribavirin. One group received high dose induction therapy with interferon followed by combination therapy and the control group received combination therapy without induction (LASER trial). This clinical trial was sponsored by Schering Plough (New Jersey, USA). Non-responders and relapsers were entered into a clinical trial evaluating response rates to different doses of interferon alfa-2b plus ribavirin. The therapeutic scheme in these two groups was determined by prior treatment with interferon, and was neither randomized nor controlled. The study was carried out at the Gastroenterology Research Unit of the University of Puerto Rico School of Medicine and the Liver Disease Clinic of the San Juan Veterans Affairs Medical Center. We present the local results unrelated to the multicenter study aims.

On satisfying all eligibility criteria, naive subjects (treatment group A, LASER participants) were randomly assigned to start an induction therapy with interferon alfa-2b (Schering-Plough) 5 MU subcutaneous injection daily for 14 days or to no induction treatment. After completing the induction phase, subjects received interferon alfa-2b

3 MU subcutaneous injection three times weekly plus ribavirin (Schering-Plough) 1000 mg (if weight was 75 kg or less) or 1200 mg (if weight was greater than 75 kg) orally and daily for 48 weeks. Subjects who did not undergo induction therapy received interferon alfa-2b plus ribavirin as previously described. Subjects were followed for 24 weeks after completion of treatment. Relapsers (treatment group B) or non-responders (treatment group C) received either interferon alfa-2b 3 MU or 5 MU by subcutaneous injection three times weekly (depending on the dose of interferon received in the prior treatment) plus ribavirin 1000 mg or 1200 mg (weight-based as previously described) orally daily for 48 weeks. Subjects were evaluated at weeks 1, 2, 4, 6, and 8; and then every four weeks during treatment. Subjects were followed at weeks 4, 8, 12, and 24 after completion of treatment (Figure 1). An untreated control group was not included because it was considered unethical in view of the accepted efficacy of combination therapy.

Figure 1. Study Scheme



Liver biopsy was performed at baseline and was analyzed to determine the presence of fibrosis, cirrhosis, and Knodell score (16). Serum HCV RNA by RT-PCR (National Genetics Institute, Los Angeles, CA), with a sensitivity of 100 copies/mL, was determined at baseline and during treatment at weeks 2, 24, and 48 on treatment group A. Serum HCV RNA by RT-PCR was determined at weeks 12 and 48 on treatment groups B and C. Biochemical and hematological testing and adverse event documentation were performed at each visit.

Adverse events were documented with severity graded as mild, moderate, severe, or life threatening. Interferon alfa-2b dose was reduced to 1.5 MU three times weekly and ribavirin dose was reduced to 600 mg daily for severe adverse events other than anemia. Ribavirin dose was reduced to 600 mg daily on subjects whose hemoglobin concentration fell below 10 g/dL and was discontinued if the hemoglobin concentration fell below 8.5 g/dL. Therapy was discontinued permanently for life threatening adverse events.

Subjects with persistent HCV RNA by RT-PCR at week 24 of treatment were considered non-responders in the study and treatment was discontinued. Those subjects who had undetectable HCV RNA at week 24 continued treatment to complete the forty-eight weeks of therapy. Relapse was defined as elevation of ALT levels and reappearance of HCV RNA during the 24-week follow-up post-treatment. Sustained virologic response in the study was defined as the absence of serum HCV RNA 24 weeks after treatment was completed. The primary endpoint of the study was to compare the rates of SVR between naive, relapsers, and non-responders to previous interferon monotherapy. The secondary endpoint was to assess combination therapy adverse events.

Patients. Hispanic patients with chronic hepatitis C, either naive, relapsers, or non-responders to previous treatment were invited to participate in the study. Naive patients were those who had never been treated before for hepatitis C. Relapsers were patients with an end-of-treatment response that relapsed after interferon monotherapy. They had normal serum alanine aminotransferase (ALT) levels or non-detectable HCV RNA by polymerase chain reaction (PCR) at the end of treatment. Post-treatment elevation of ALT or reappearance of HCV RNA followed. Non-responders were patients with no response to interferon monotherapy. These patients had HCV RNA present in serum or elevated serum ALT levels after at least 12 weeks of interferon monotherapy (9). Most of the previously treated patients had been classified based only on biochemical response, as detection of RNA was not performed routinely at the time of initial treatment. Patients with detectable serum HCV RNA with a reverse transcriptase-PCR (RT-PCR), a liver biopsy with chronic hepatitis prior to the treatment, and elevated serum ALT values for at least the previous six months were eligible for the study. Patients with decompensated cirrhosis, serum alpha-fetoprotein greater than 50 ng/mL, anemia (hemoglobin concentration less

than 12 g/dL in women and less than 13 g/dL in men), human immunodeficiency virus infection, psychiatric disorders, or seizure disorders were excluded from the study. Patients with cardiovascular disease, hemophilia, poorly controlled diabetes mellitus, autoimmune disease, liver transplantation, or unable to use contraception during the study were also excluded from the study.

The Institutional Review Boards of the University of Puerto Rico Medical Sciences Campus and the San Juan Veterans Affairs Medical Center approved the study. All patients provided written informed consent before entering the study.

Statistical analysis. Descriptive statistics for continuous variables including mean and standard deviation were computed. Frequency distributions and percents were used for categorical variables. The Shapiro Wilk test was used to evaluate the normal assumption of quantitative variables. To determine statistical associations among categorical variables, and to compare the response rates (sustained response, relapse and no response) for each treatment group, the Pearson's chi-square test or Fisher's exact test, when appropriate, was used. Unadjusted relative risk (RR) and 95% confidence limits (95% CI) were calculated to estimate the magnitude of the associations among fibrosis and treatment group (relapsers, non-responders and naive). To compare continuous variables such as age, HCV RNA, baseline ALT serum levels and Knodell score between the three treatment groups (naive, responders and non-responders), the analysis of variance (ANOVA) or Kruskal Wallis test, when appropriate, was used . All statistical tests were two-sided. A p value of less than 0.05 was considered of statistical significance. Data entry was performed using Epi-Info 6.04d . The SAS and STATA packages were used to perform the statistical analysis.

Results

Between November 1997 and February 2000, 167 subjects were allocated to the treatment groups: 57 to group A, 42 to group B, and 73 to group C. Five patients in group B were removed from the analysis for dropping out after the first evaluation. Response could not be determined in 27% of subjects lost to evaluation during treatment or follow-up 24 weeks post-treatment: 15/57 (26%) naive, 11/37 (30%) relapsers, and 19/73 (26%) non-responders (p=0.91).

The majority of the subjects were males (57.6%). No significant difference was found among the three treatment groups regarding age, sex, baseline ALT, or baseline HCV RNA ($p > 0.05$). There was no significant difference among the treatment groups when compared for the presence of cirrhosis and Knodell score at baseline ($p > 0.05$). The presence of fibrosis was significantly higher in naive subjects (74.1%), followed by non-responders (46.6%) and relapsers (37.0%) ($p < 0.001$) (Table 1).

Table 1. Baseline Characteristics of the Three Groups

	Naive (n = 57)	Relapsers (n = 42)	Non-responders (n = 73)	p value
Demographics				
Mean age (years)	45.7±9.5	45.8±9.2	46.5±8.7	> 0.05
Gender (male / female)	38/19	23/19	38/35	> 0.05
Liver function test (normal: 7-40)				
Serum ALT levels (IU/L)	138.0±125.2	145.0±123.4	155.0±162.5	> 0.05
Viral load				
Serum HCV RNA (* 10^6 copies/ml)	3.4±2.3	2.6±2.0	2.9±2.0	> 0.05
Histology				
Knodell score	9.3±3.2	2.8±3.2	9.5±4.1	> 0.05
Fibrosis (%)	74.1	37.0	46.6	< 0.001
Cirrhosis (%)	24.1	44.4	32.1	> 0.05

ALT: alanine aminotransferase. HCV RNA: hepatitis C virus ribonucleic acid.

Table 2 shows the associations between the treatment groups and fibrosis risk. The relapsers and the non-responders groups were significantly associated with less risk of fibrosis (RR=0.30, 95%CI = 0.14-0.68, p = 0.004 and RR=0.21, 95%CI = 0.07-0.55, p = 0.002, respectively) than the naive group.

Table 2. Association Between Treatment Groups and Fibrosis

Treatment	RR*	95% CI*	p-value
Relapsers	0.30	(0.14 - 0.68)	0.004
Non-responders	0.21	(0.07 - 0.55)	0.002
Naïve1	.00	-	

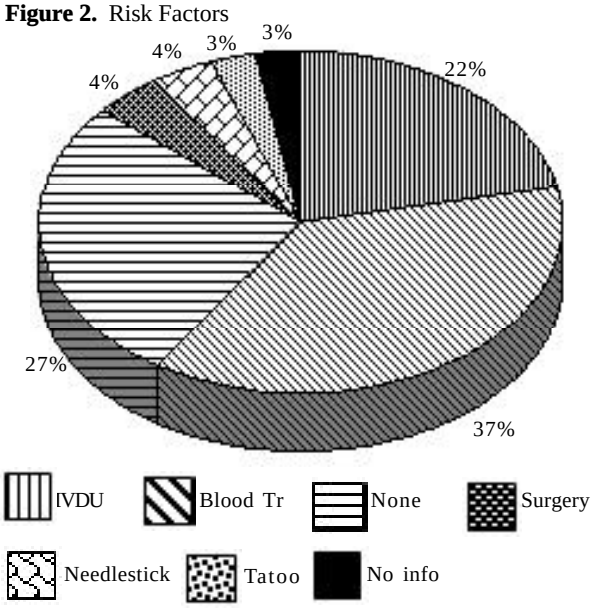
*Relative risk and 95% confidence interval

The most common risk factors for HCV infection reported were blood transfusion (37%) followed by injecting drug use (22%). A high proportion of the subjects did not identify a risk factor (27%) (Figure 2).

The most frequent adverse event was anemia (89%), followed by fever (68%), and fatigue (66%). These adverse events occurred in the majority of subjects (Figure 3).

SVR was achieved in 23% of naive subjects, 45% of relapsers, and 8% of non-responders. This response difference was significant among the three treatment

Figure 2. Risk Factors



groups ($p < 0.001$, Figure 4). No difference was found between the response rate of naive patients receiving induction therapy and those without induction. Relapse in the 24 weeks after treatment was found in 14% of naive subjects, 4% of relapsers, and none of non-reponders. The difference among the treatment groups was marginally significant ($p = 0.057$). No response to combination therapy was observed in 40% of naive subjects, 22% of relapsers, and 62% of non-responders. A significant difference was obtained ($p < 0.001$) .

Figure 3. Side Effects

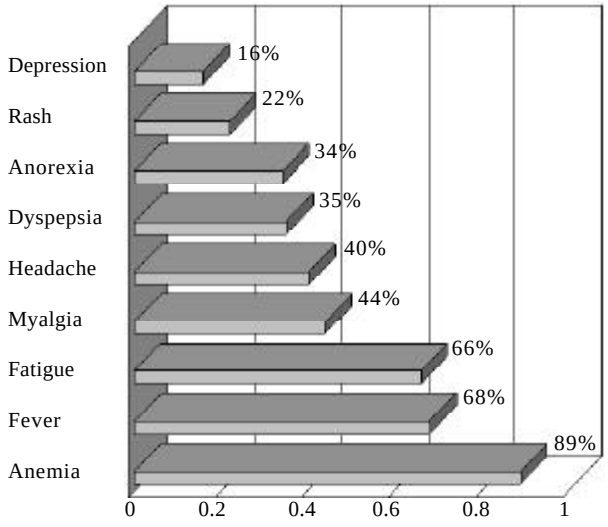
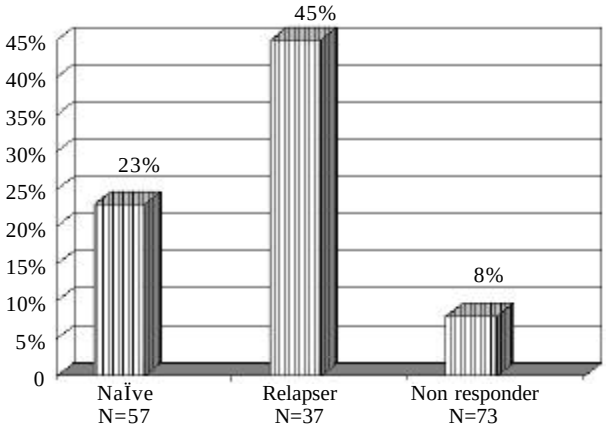


Figure 4. Sustained Response



P<0.001

Discussion

This study shows that Hispanic patients with chronic hepatitis C have a low SVR rate to combination therapy of interferon alfa-2b plus ribavirin. Previous studies demonstrated a high prevalence of HCV genotype 1 in Puerto Rico. Studies performed by Rodríguez-Medina et al. (personal communication) using restriction fragment length polymorphism (RFLP) analysis of 5' non-coding region (5'NCR) products (17) in a similar Puerto Rican population showed that 74% of HCV patients had genotype 1. Unpublished observations by Castro et al. (2001) revealed that 89.5% of Puerto Rican HCV patients had genotype 1. A study by Rodríguez-Pérez et al. revealed that 83% of Puerto Rican HCV patients had genotype 1 (18). Genotype 1 accounts for 70-75% of all HCV infections in US and is associated with a lower rate of response to treatment than other genotypes (5). The observed prevalence of HCV genotype 1 in Hispanics in Puerto Rico is higher than reported in other populations: Caucasians with 65%-66% and Hispanics not residents of Puerto Rico with 68%-78%. African Americans have a prevalence of HCV genotype 1 of 87%-96% (12, 13).

Hispanics treated with combination therapy as initial therapy for chronic hepatitis showed 23% SVR rate. This rate is lower than the SVR reported previously to combination therapy for naive patients, which ranges from 37% to 67% (19-24). It is also lower than naive Caucasians (42%-49%) (25) and similar to naive African Americans (23%) (13). Relapser patients showed a SVR rate of 45%, which is similar to previous reports that show a SVR ranging from 42% to 75% for relapsers (19-22, 24). The higher response rate of relapsers as compared to naive patients is not unexpected since these patients have already shown a response to interferon monotherapy. Patients who failed to respond to interferon monotherapy

are a group of special concern. Only 8% of these patients had a SVR to combination therapy, lower than previous studies that show a SVR ranging from 12.6% to 25% for non-responders (19-22, 24, 26-29) (Table 3).

Table 3. Sustained Response to Interferon Plus Ribavirin for chronic Hepatitis C.

	Naive(%)	Relapsers(%)	Non-responders (%)
Muñoz et al.	23	45	8
Schalm et al[19]	52	60	21
Schalm et a[20]	67	75	25
Schalm et al[21]	52	52	19
Shepherd et al[22]	41	49	NS
Poynard et al[23]	41	NS	NS
Kjaergard et al[24	37	42	15
Cheng et al[26]	NS	NS	21.3
Cummings et al[27]	NS	NS	14
Cammà et al[28]	NS	NS	15.7
San Miguel et al[29]	NS	NS	12.6

NS: not stated.

Patient and viral factors have been associated with SVR in chronic hepatitis C. HCV genotype 2 or 3, serum HCV RNA levels less than 3.5 million copies/mL, no bridging fibrosis or cirrhosis on liver biopsy, age less than 40 years old, female gender, and low body weight have been associated to a better response rate (30). Early virologic response (loss of HCV RNA or its decrease by at least two log-folds as compared with baseline values) (31) and adherence to therapy have been also been associated to a better response (30).

Anemia was the most commonly reported adverse event (89%), more frequent than in previous reports (9). This adverse event impacts compliance with therapy, as well as increasing cost if erythropoietin is used to allow continuation of therapy. Ribavirin may cause anemia due to hemolysis. Hemoglobin levels must be followed carefully throughout therapy. Erythropoietin is effective in maintaining desirable hemoglobin levels when significant hemolysis occurs (4). Fever, fatigue, and myalgia followed as the most commonly reported adverse events, consistent with the literature (7). The study significance is limited by the small number of patients studied. Future studies should include a larger number of patients.

The current standard of care for treatment of chronic hepatitis C is pegylated interferon alfa-2a (180 μg per week) or 2b (1.5 μg/kg per week) in combination with ribavirin. New promising medications are under study. Putative antifibrotic medications like interferon gamma are currently being evaluated. RNA polymerase, helicase, and protease (proteins necessary for HCV multiplication) inhibitors are in early-phase trials. HCV vaccine development programs are under way (4).

In conclusion, Hispanic naive and non-responder patients with chronic hepatitis C have a lower sustained virologic response rate to combination therapy of interferon alfa-2b plus ribavirin than previous reports. Hispanic relapser patients have sustained virologic response similar to other studies. Response rate to pegylated interferon plus ribavirin in our Puerto Rican population is currently under evaluation. Individuals who are uninsured or have publicly funded healthcare are more likely to be infected with HCV, and Hispanics make up a high proportion of them. The role of ethnicity as a possible factor that can influence the chance of response to combination therapy needs to be determined in order to design more effective treatment for this population. Future treatment protocols for chronic hepatitis C must consider an adequate representation of this ethnic group.

Resumen

El virus de la hepatitis C puede llevar a una infección crónica y a múltiples complicaciones. La respuesta a la terapia de combinación de interferón y ribavirina ha sido estudiada en muchas poblaciones. Los africano-americanos tienen una tasa de respuesta más baja que los caucásicos. Sin embargo, pocos datos existen sobre hispanos. Los objetivos de este estudio fueron evaluar la respuesta de los hispanos con hepatitis C crónica a la terapia de combinación de interferón alfa-2b y ribavirina y sus eventos adversos. Pacientes hispanos de Puerto Rico con hepatitis C crónica fueron elegibles para el estudio entre noviembre de 1997 y febrero de 2000. Las Juntas de Revisión Institucional de las instituciones participantes aprobaron el estudio. Se obtuvo consentimiento informado por escrito. La terapia de combinación fue dada por 48 semanas y los pacientes fueron seguidos por 24 semanas después del tratamiento. El análisis de la respuesta a la terapia se realizó basado en la intención de tratar. El evento adverso más frecuente fue anemia (89%), asociada a ribavirina. La respuesta sostenida fue de 23% para los pacientes no tratados antes, 45% para los pacientes que recayeron luego de monoterapia previa de interferón y 8% para los pacientes que no respondieron a la monoterapia previa ($p < 0.001$). Datos para analizar respuesta no estuvieron disponibles en 27% de los pacientes. Los pacientes hispanos tuvieron una baja tasa de respuesta a la terapia de combinación. Esto puede ser debido a una alta prevalencia del genotipo 1, asociado a pobre respuesta, en Puerto Rico. Las tasas de respuesta a la terapia de combinación para los pacientes hispanos no tratados antes y para los que no respondieron a la monoterapia previa de interferón fueron menores a las de otras poblaciones reportadas. Una mayor tasa de respuesta

de los que recayeron, similar a la reportada previamente, era esperada ya que estos pacientes habían demostrado una respuesta previa a la monoterapia de interferón. Factores étnicos podrían jugar un papel en la respuesta a la terapia y deben ser estudiados más a fondo para determinar estrategias de tratamiento apropiadas para esta población.

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