Sustained Virologic Response among Latino Veterans; Does it Represent the Cure of Chronic Hepatitis C Infection?

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Objective: Short-term benefits of achieving sustained virologic response (SVR) to treatment for hepatitis C virus infection (HCV) have been well established. However long-term data on benefits of achieving SVR has just begun to emerge. The purpose of this study was to determine whether SVR truly represents long- term viral eradication in a Latino veteran population and document clinical and biochemical outcomes in this group.

Methods: This was a two-phase study, which consisted of a single center retrospective study followed by a cross-sectional analysis which includes a single clinic visit. The first phase of the study consisted of a retrospective record review of all HCV patients treated at the VA Caribbean Healthcare System from 1990 to 2006. Records were reviewed to identify patients who had completed therapy, had documented SVR and at least 12 months of time elapsed since end of therapy. The second phase of the study entailed a single appointment to the gastroenterology research clinics, for blood testing and a short risk factor questionnaire.

Results: Sixty four patients were enrolled; mostly males with a mean age at time of enrollment of 54.3 years (range 37-72). One hundred percent of subjects self reported their ethnicity as Hispanic, born in Puerto Rico. Most of our population had HCV genotype 1. Forty seven of 64 (73.4%) patients were naive to therapy while 4 (6.3%) were previously treated. In 13 (20.3%) patients, the prior treatment status could not be clearly established. Regarding therapy used to achieve SVR, 32 (50.0%) patients received interferon (IFN) and ribavarin, 28 (43.8%) peginterferon (PEG) and ribavarin and 4 (6.3%) IFN monotherapy. There was no statistical difference in long-term SVR among these 3 three treatment alternatives. A pre-treatment biopsy specimen was available on 37/64 (57.8%) of our subjects. Marked fibrosis and/or cirrhosis was present in 14/37 (37.8%) subjects who had a pre-treatment biopsy. At the time of the study visit mild elevation of aspartate aminotransferase (AST) was identified only in 5 (7.8%) patients. Alanine aminotransferase (ALT) and bilirubin were normal. Only 3/64 (4.7%) had elevations in alkaline phosphatase. None (0/58) of the patients who presented with normal enzymes had detectable viral load, whereas 20% (1/5) of those with elevated liver function tests had evidence of viremia ($p < 0.001$). Overall, only 1 (1.6%) patient of our study group had evidence of virological relapse after having achieved SVR, which was documented 30 months after the end of therapy. No identifiable risk factors for re-infection were identified.

Conclusion: In conclusion, in this Latino veteran population, achievement of (SVR) is a good predictor of clinical outcomes and long-term (HCV) eradication. Altered liver function tests seems to be the best predictor of relapse and should prompt the clinician to investigate for recurrence. For those that after achieving SVR maintain normal liver enzymes, routine follow up viral load demonstrates to have a very low yield and may not be required. [*P R Health Sci J 2010;4:397-401*]

Key words: Hepatitis C, Chronic, Outcome Assessment, Hispanic Americans

The primary goal of therapy for hepatitis C virus (HCV) is to eradicate infection early to avoid progression to end stage liver disease and the development of hepatocellular carcinoma (HCC). Effectiveness of treatment is determined by documenting sustained virologic response (SVR), which is defined as absence of detectable virus in serum 6 months

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after completion of therapy. Those patients achieving SVR are expected to remain free of disease thereafter. Short-term benefits of achieving SVR have been very well established (1), however long-term data on benefits of achieving SVR have just begun to emerge. It has been recognized that the majority of patients who achieve SVR have good clinical outcomes with overall survival rates similar to non HCV infected individuals (2-3), however very limited data exists on the benefits of long-term SVR in Latino populations which according to the U.S. Census Bureau currently represent the largest minority group in the USA (4). Seroprevalence studies of HCV among Latinos are higher than their Caucasian counterparts (5), and among Puerto Ricans the seroprevalence has been reported as high as 6.3% (6). Overall, Latinos have documented lower therapy response rates (7), are less likely to begin HCV therapy (5), and have twice the mortality rates when compared to non-latino whites (8). Data concerning SVR outcomes in U.S. veterans has been particularly disappointing with Morelli et al. reporting a low 10% SVR (9), highlighting the importance of acquiring further knowledge about this group. Our goals were to determine whether SVR truly represents long-term viral eradication in a Puerto Rican veteran population and to document clinical and biochemical outcomes in this group.

Patients and Methods

This was a single center retrospective study followed by a cross-sectional analysis which includes a single clinic visit. Approval to conduct a two-phase study, single center retrospective followed by a cross-sectional analysis which included a single clinic visit, was obtained from the Institutional Review Board. The first phase of the study consisted of a retrospective record review of all patients treated with interferon (INF) or pegylated interferon (PEG) either with or without ribavirin at the VA Caribbean Healthcare System from 1990 to 2006. Patients were identified through the pharmacy documentation of dispensing INF, PEG or ribavirin. Records were reviewed to identify patients who had completed treatment with any of the following therapies for hepatitis C: interferon (INF) monotherapy (3 MU TWI), standard combination therapy (INF 3MU TWI with weight based interferon), pegylated interferon (PEG) (alpha-2a or alpha-2b) monotherapy or in combination therapy with weight based ribavirin. Those who had documented sustained viral response (SVR) and had completed therapy at least 12 months prior to the record review were considered candidates for enrollment in the second phase of the trial. The second phase entailed a single appointment to the gastroenterology research clinics, where all subjects were consented for participation. At this visit a short questionnaire was completed with the purpose of evaluating past compliance to therapy, and exclude recent risk factors for HCV re-infection (major o minor surgery, drug use, tattoos, and high-risk sexual behavior). The questionnaire also assessed for long-term complications of liver disease including development of ascites, hepatic encephalopathy, variceal bleeding or hepatocellular carcinoma. Child-Pugh classification was also documented. Blood samples for HCV viral load by PCR (Roche Cobas AmpliPrep Taqman HCV test), hemoglobin, white blood cell count, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, partial thromboplastin time (PTT), prothrombin time (PT) and total bilirubin were taken. Demographic information was obtained from the medical record, and pretreatment liver biopsies when available were also evaluated. Total time from end of treatment to study enrollment was obtained from medical records and confirmed with study participants at the time of interview.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (SPSS Inc, Chicago Illinois, USA). Chi-square test was used to determine associations between SVR and other variables. Age, sex, HCV genotype, ALT, AST, and were analyzed. The decision criteria for association was a p value <0.05. Multivariate analysis was used to highlight factors that may impact the outcome of long term SVR.

Results

Patient Demographics and treatment

One hundred and eighty-nine patients' records were reviewed; of those, 73 met the inclusion criteria. The eligible patients were then contacted by phone and invited to participate. Sixty-four patients consented to participate in the second phase of the study, all of whom completed therapy and had documented SVR through the Veterans Administration hospital facilities in Puerto Rico from 1990 to 2006. All patients completed a one-time follow up visit, where patients were interviewed, a questionnaire was completed, and blood samples were drawn.

The mean age at time of enrollment was 54.3 years (range 37-72), 100% of subjects self reported their ethnicity as Hispanic, born in Puerto Rico. Given the nature of our population the study group consisted of 63 (98.4%) males and 1 (1.6%) female. Most of our population had HCV genotype 1, which is the most common genotype in Puerto Rico (10) (Table 1).

Table 1. Distribution of HCV genotypes among study group

Genotypes	No.	Percent
1	35	54.7%
2	17	26.6%
3	3	4.7%
4	1	1.6%
Not available	8	12.5%
Total	**64**	**100.0%**

Forty-seven of 64 (73.4%) patients were naive to therapy while 4 (6.3%) were previously treated. In 13 (20.3%) patients, the prior treatment status could not be clearly established.

Our population received various treatment modalities mainly due to the long period of evaluation. Seventy-seven (67) percent of the patients had completed therapy 3 to 6 years prior to enrollment. The distribution of treatment modalities was as follows: 32 (50.0%) patients received IFN and ribavarin, 28 (43.8%) PEG and ribavarin, and 4 (6.3%) IFN monotherapy. There was no statistical difference in long-term SVR among the 3 treatment alternatives. The variation in therapy reflected the advances in therapy and guidelines adherence over time.

Baseline histological assessment

A pre-treatment biopsy specimen was available for 37/64 (57.8%) subjects. Marked fibrosis and/or cirrhosis was present in 14/37 (37.8%) subjects.

Among the 14 patients with severe fibrosis or cirrhosis the mean follow up time was 34.0 ± 17.7 months. There was no statistical significance between HCV genotype and histological assessment (Table 2).

Table 2. Histological findings according to HCV genotype.

Genotype	No Biopsy	Histology		Total
		Mild/Moderate fibrosis	Marked fibrosis/ cirrhosis	
Not available	8			
1	12	17	6	35
2	7	6	4	17
3	-	-	3	3
4	-	-	1	1
Totals	**27**	**23**	**14**	**64**

Virologic, biochemical and clinical outcomes

At the time of the study visit, elevation of AST was identified only in 5 (7.8%) patients and this elevation was modest in all, with AST average of 59.4 ± 12.3 U/L (normal values 0-45 U/L). ALT and bilirubin were normal in all subjects. Only 3/64 (4.7%) had elevations in alkaline phosphatase. None (0/58) of the patients who presented with normal enzymes had detectable viral load, whereas 20% (1/5) of those with elevated liver function tests had evidence of viremia. Overall, only 1 (1.6%) patient of our study group had evidence of virologic relapse after having achieved SVR, which was documented 30 months after the end of therapy. No identifiable risk factors for re-infection were identified.

The average follow up time from end of treatment to time of enrollment was 36.9 ± 14.1 months (range 15 - 79). Twenty nine (45.3%) of our patients had at least 36 months of follow-up time and 10 (15.6%) had at least 48 months of follow up.

A total of 7 patients (10.9%) developed diabetes after completing hepatitis C therapy and achieving SVR. Among other clinical diagnosis assessed after end of therapy, only one patient (1.6%) reported lower gastrointestinal bleeding, however this patient also had a diagnosis of ulcerative colitis, and only one patient (1.6%) reported new onset kidney disease. None of the 64 patients had any severe clinical outcome defined as ascites, encephalopathy, variceal bleeding or hepatocellular carcinoma either self documented or identified by record review.

Discussion

This study demonstrates that in our Veteran Latino population there is a very low relapse rate after SVR is achieved, regardless of the treatment received or HCV genotype. Also of great importance is the fact that liver disease related clinical events were absent, again supporting good long term outcomes once SVR has been achieved. Nevertheless, supporting data in Hispanic patients has been very limited. The durability of SVR in our population is similar to that reported for other ethnic groups and supports the fact that SVR continues to be our best method to assess long-term viral clearance. A recent study conducted in the United States evaluating long-term clinical outcomes in a population of 150 patients with SVR, showed similar results.2 In addition, our study demonstrates that long-term durability of this response once SVR is documented is independent of the therapy with which this was achieved.

This study also supports the evidence that routine follow up viral loads after SVR has been documented are of low yield, and probably indicated only in patients with altered liver function tests. None of our patients with SVR developed hepatocellular carcinoma over an average 36.9 month follow up time despite the fact that 37.8% of subjects had severe fibrosis or cirrhosis on pre-treatment biopsy. This fact highlights the importance of SVR on overall HCV-related morbidity and mortality. New onset diabetes mellitus was seen in 10.9% of patients which is similar to long- term data published by other authors (11-12).

The aim of this study was to answer a common question physicians encounter in their daily practice when treating patients with chronic HCV infection: Would the infection recur after having achieved a sustained response? The response appears that it would not in most of the patients. We could not focus on type of treatment received, viral load, or patient genotypes. Nonetheless, in our study 54% of the patients had genotype 1, while 30% of the patients had genotype 2 or 3. This represents an expected over expression of genotype 2 and 3 patients since these genotypes are more responsive to therapy than genotypes 1 and 4. A previous study about our population has demonstrated that the prevalence of HCV genotypes is 82% for type 1 and 18% for non-1 genotypes (10).

One of the limitations of our study is that patients were retrospectively selected for which multiple variables could not be controlled; nevertheless no deaths were identified within

the pool of patients with SVR and only 9 of the 73 patients identified through record review could not be reached and/or enrolled in the second phase of the study. In addition, the retrospective identification of patients and cross-sectional analysis, did not allow to asses outcomes in patients who had achieved SVR and relapsed who did not choose to participate in the study. Furthermore, our study group does not allow to draw any conclusions in female patients due to the male predominance in our group. Prospective studies are needed to evaluate long-term complications in patients with HCV who have achieved SVR.

In our study, the possibility of re-infection in the single patient that demonstrated measurable viral load cannot be totally disregarded, however risk factors for re-infection were thoroughly evaluated with the questionnaire administered at the time of protocol enrollment. The possibility of non-detectable viremia at end of treatment or at 6 months follow up could be related to the higher threshold value of 600 copies used years ago, in comparison to newer assays, which have a much lower detection limit of 50 copies.

In conclusion in this Latino veteran population, achievement of SVR is a good predictor of clinical outcomes and long-term viral eradication. Altered liver function tests seems to be the best predictor of relapse and should prompt the clinician to investigate for recurrence. For those that after achieving SVR maintain normal liver enzymes, routine follow up viral load demonstrates to have a very low yield and may not be required.

Resumen

Objetivo: Los beneficios a corto plazo de alcanzar una respuesta sostenida en la erradicación de hepatitis C están bien documentados, pero el efecto de ésta a largo plazo aún está investigándose. El propósito de éste estudio fue determinar el efecto a largo plazo de la respuesta viral sostenida y documentar los efectos clínicos y bioquímicos en este grupo de pacientes. Métodos: Este estudio consistió de dos partes y se realizó en un solo centro. La primera fase consistió de la evaluación retrospectiva de los expedientes médicos de pacientes tratados para hepatitis C en el Sistema de Salud de Veteranos del Caribe durante el periodo de 1990 a 2006. Se identificaron pacientes que completaron tratamiento, adquirieron una respuesta sostenida y que hubiera pasado al menos un año desde que hubiera terminado el tratamiento. La segunda fase consistió en invitar al paciente a una visita médica, donde se realizaron pruebas de sangre y se le administró un cuestionario corto. Resultados: Sesenta y cuatro pacientes fueron reclutados. Eran hombres mayormente con una edad promedio de 54.3 años. El 100% reportó haber nacido en Puerto Rico y se catalogó como hispano. La mayoría de la población tenía genotipo 1. Cuarenta y siete (73.4%) de los pacientes habían sido tratados por primera vez, mientras que 4 (6.3%) habían sido ya tratados anteriormente; en los otros no se pudo establecer. En cuanto a la terapia usada, 32 (50.0%) de los pacientes recibieron interferón (IFN) y ribavarina, 28 (43.8%) peginterferón y ribavarina y 4 (6.3%) monoterapia con interferón. No hubo diferencias entre los grupos y la terapia recibida. Sólo 14/37 (37.8%) de los pacientes tenían una biopsia de hígado previa a tratamiento. Cirrosis o fibrosis marcada estaba presente en 14/37 (37.8%). Al momento de la visita, solo 5 (7.8%) pacientes tenían elevación leve de la AST. La bilirrubina y el ALT fueron normales. Sólo 3/64 (4.7%) tenían elevación leve de la fosfatasa alcalina. Ninguno de los pacientes con enzimas normales demostró presencia de carga viral, mientras que 20% (1/5) de los que tenían AST elevados sí. En general, sólo un (1.6%) paciente demostró recurrencia de la hepatitis C, documentándose ésta 30 meses luego de haber completado la terapia. No se identificaron factores de riesgo para la re-infección. Conclusión: En esta población de pacientes latinos con hepatitis C, el obtener una respuesta viral sostenida inicial es un buen marcador de respuesta sostenida a largo plazo. Tener una prueba hepática alterada parece ser el mejor predictor de recurrencia y debe alertar al médico de la necesidad de investigar para una posible recurrencia. Para aquellos que obtienen una respuesta viral sostenida y mantienen sus pruebas hepáticas normales, el realizar pruebas de carga viral a largo plazo tienen un valor bajo y parecen no ser necesarias.

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