ARTÍCULO ORIGINAL

Prevalence of hepatitis C virus genotypes in Mexican patients

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SUMMARY Background: *Worldwide HCV studies have documented its large genetic variability; HCV has major genetic groups called genotypes that are designated from 1 to 6, as well as > 50 subtypes. This is very important considering that treatment response varies according to genotype. The purpose of this trial was to ascertain prevalence of HCV genotypes in a group of patients from 10 states in Mexico.* ***Methods:*** *This study enrolled patients from 22 hospitals throughout the country. Patients tested positive to hepatitis C antibody and genotyping was preformed by Lipa method. To carry out a comparison, two regions were arbitrarily defined, the northern region embodied the cities of Culiacan, Torreón, Monterrey, Ciudad Obregón, and Tijuana, while the central-southern region embodied Mexico City, Guadalajara, León, Puebla, and Veracruz.* ***Results:*** *The test was performed on a total of 421 patients. The most frequently found genotype was genotype 1, present in 70.55% of cases. The majority (40.1%) corresponded to genotype 1b, 17.81% to 1a, and genotype 2a/2c (11.64%). A total of 29.4% of samples corresponded to genotypes non-1. Genotype 1 was found in 72.34 (northern region) and 70.03% (central-southern) of the two regions, and genotypes non-1 in 27.66 and 29.97%, respectively.* ***Conclusions:*** *We conclude that the most frequent genotype in Mexico is 1b, followed by 1a, and, in third place 1b1a, for a total of 70.55%; the remaining 29.45% had genotypes other than 1.*

Key words: *Chronic hepatitis C, genotypes, Mexican population*

RESUMEN Antecedentes: *los estudios a nivel mundial del virus de la hepatitis C (VHC), han documentado una gran variabilidad genética. El VHC tiene grupos genéticos mayores llamados genotipos que se han designado del 1 al 6, así como más de 50 subtipos. Esto es sumamente importante ya que la respuesta al tratamiento varía de acuerdo al genotipo. El propósito de este estudio fue investigar la prevalencia de los genotipos del VHC en un grupo de pacientes de 10 estados en la República Mexicana.* ***Métodos:*** *este estudio incluyó pacientes de 22 hospitales de diversos lugares de nuestro país. Los enfermos tenían el anticuerpo C positivo y el genotipo se determinó por el método de Lipa. Con objeto de hacer una comparación se definieron arbitrariamente dos regiones, la región norte que incluyó las ciudades de Culiacán, Torreón, Monterrey, Ciudad Obregón y Tijuana; y la región central sur que incluyó Ciudad de México, Guadalajara, León, Puebla y Veracruz.* ***Resultados:*** *la prueba se efectuó en un total de 421 pacientes. El genotipo que se encontró con mayor frecuencia fue el 1 que se presentó en 70.55% de los casos. La mayoría (40.1%) correspondió al 1b, 17.81% al 1ª y genotipo 2ª/2c (11.64%). El 29.4% de las muestras correspondieron al genotipo no 1. El genotipo 1 se encontró en 72.34% de la región norte y en 70.03% de la región centro sur, y el genotipo no 1 se encontró en 27.6% y 29.97% respectivamente.* ***Conclusiones:*** *se concluye que el genotipo más frecuente en México es 1b seguido por el 1ª y en tercer lugar 1b1a, para un total de 70.55%, 29.45% restante tuvieron un genotipo diferente al 1.*

Palabras clave: *Hepatitis crónica C, genotipos, población mexicana.*

INTRODUCTION

Globally, an estimated 170 million people are infected with hepatitis C virus.[1] This high tendency of hepatitis C virus to develop into chronic infection is partly due to the virus's own characteristics, such as high mutation tendency,[2] may partly explain why despite the wide range of existing therapeutic schemes there is no favorable response in a significant number of cases.[3]

Genetic variability is one of the most relevant findings of hepatitis C virus (HCV) genome, which does not correspond to the entire genome. Most preserved regions have been identified in portions such as 5' NC and terminal region 3' NC. The most preserved reading frame region consists of capside proteins followed by proteins of NS3 and NS5B regions. The most heterogeneous regions in the genome are those encoding for two envelope proteins, E1 and E2. HCV heterogeneity is very complex and has been classified in genotypes, subgenotypes and quasispecies.[4]

HCV trials through around the world, a significant genetic variation has been documented.[5] Based on such variation, the existence has been acknowledged of major genetic groups of HCV, called genotypes, which in turn are subdivided into subgroups called subgenotypes or subtypes. A total of six major genotypes, designated sequentially according to their disclosure order from 1 to 6, exists; > 50 subtypes have been identified and designated with lower-case letters in the order of their disclosure for each genotype.[6-8]

Response to treatment will be different depending on genotype and, additionally, that treatment duration may vary according to genotype.[9] Recent studies have suggested that patients with genotype 1 should receive pegylated interferon alpha plus ribavirin for 1 year, and patients with genotype non-1 only for 6 months, thus the importance of knowing the genotype prior to making a decision about treatment for a particular patient.[10]

Genotype prevalence is of major importance to be known in Mexican population as to date its prevalence has been documented only specific geographic regions.[11] The purpose of this trial was to ascertain prevalence of HCV genotypes in a group of patients with chronic hepatitis C from 10 states of the Mexican Republic.

TABLE 1
RESULTS OF VIRAL GENOTYPING

Genotype	N	%
1	12	2.8
1a/1b	41	9.74
1a	75	17.81
1b	169	40.14
Total Genotype 1	297	70.55
2	4	0.95
2a	6	1.43
2b	38	9.03
2a/2c	49	11.64
3	2	0.48
3a	22	5.23
3b	1	0.24
4	2	0.48
Total Genotype Non-1	124	29.45
TOTAL	421	100

MATERIALS AND METHODS

Screening tests were performed from June 1998 to February 2002 on patients with chronic hepatitis C in 22 hospitals throughout the Mexican Republic *(Appendix 1)* to assign patients to one of six different multinational clinical trials for development of peginterferon alpha-2a (40KD) (PEGASYS®).[12-17] All patients tested positive to HCV antibodies by enzymatic immunoassay (ELISA) and were assayed for HCV genotype. Samples were assayed, depending on the trial, at one of five different laboratories (GENOMA, México; CIF-Biotec, México; UCTI Laboratories, USA; ICON Laboratories, USA; and QUEST, USA).

All genotype tests were performed by Lipa method (formerly known by the trade name Inno-Lipa by Innogenetics Inc., currently Versant HCV Genotype Kit by Bayer Diagnostics). This test's principle is based on reverse hybridization with oligonucleotide probes representing specific sequences patterns in HCV region 5' NCR. Viral genotyping is carried out using an interpretation table containing 60 individual patterns, each of which is specific for one genotype or subtype. Taking into account the considerable heterogeneity of HCV sequence, it is very unusual to observe patterns of non-interpretable strands.[18]

TABLE 2
RESULTS BY REGION

	Northern Region		Central-Southern Region	
Genotype	N	Percentage	N	Percentage
1	4	4.26	8	2.45
1a/1b	16	17.02	25	7.65
1a	19	20.21	56	17.13
1b	29	30.85	140	42.81
Total Genotype 1	68	72.34	229	70.03
2	0	0.0	4	1.22
2a	4	4.26	2	0.61
2b	5	5.32	33	10.09
2a/2c	3	3.19	46	14.07
3	2	2.13	0	0
3a	9	9.57	13	3.98
3b	1	1.06	0	0
4	2	2.13	0	0
Total Genotype Non-1	26	27.66	98	29.97
TOTAL	94	100	327	100

To compare genotype frequency in geographic areas, the country was divided into two arbitrarily defined regions. The region called northern embodies the cities of Culiacan, Torreon, Monterrey, Ciudad Obregon, and Tijuana, and the region named central-southern embodied the cities of Guadalajara, León, Puebla, Veracruz and Mexico City. Chi square test was performed to compare the ratio between geographic regions.

RESULTS

Viral genotyping was performed in a total of 421 patients with hepatitis C; the results obtained are shown in *table 1*. The most frequently found genotype was genotype 1, present in 70.55% of cases. The majority (40.1%) corresponded to genotype 1b, 17.81% to 1a, and genotype 2a/2c (11.64%). A total of 29.4% of samples corresponded to genotypes non-1.

When analysis comparing the two different geographic regions (northern and central-southern) was carried out, similar distribution was observed: 70.3% with genotype 1, and 29.9% with genotype non-1. Results by region are shown in *table 2*. There was no significant difference between the two groups ($p = 0.761$). From 421 reported patients, only two had genotype 4, both from the city of Monterrey, and with genotype 3, there were 12 patients from the northern region, and 13 patients from the central-southern region, 12.7 and 3.9% respectively.

DISCUSSION

As the results of this trial showed, the most frequent genotype in Mexico was genotype 1, ype 1b prevailing which is consistent with previous reports from small-scale studies performed in Mexico, and with data reported in the literature. Grouping all patients with genotype 1 in its different combinations i.e., 1a, 1a and 1b, or 1b, 70% of these patients evaluated was embodied; however, 30% of patients had genotype non-1, the most frequent being genotype 2, with a small proportion with genotype 3, and only two cases with genotype 4.

These findings are of major importance because as previously noted it has been recently reported that patients with genotype non-1, mainly genotype 2 and 3, may be treated with high response, > 70%, with pegylated interferon alpha 2a plus a fixed daily dose of ribavirin (800 mg), obviously reducing costs and drug side-effects. On the other hand, in patients with genotype 1 therapy may be evaluated for 12 weeks, after which a 2-log viral load reduction from baseline must be achieved or become negative Otherwise it is not worth continuing treatment, as no response to treatment is likely while although therapy continues for 1 year; with significant impact on management costs for these patients. It was

also shown that genotype is the most important predictor of response to treatment, even more than viral load and other factors such as race, gender, and age at infection.[19,20]

Mahaney, et al.[21] examined hepatitis C virus genotypes in 98 American patients with chronic hepatitis C virus infection. They found that type 1 was present in 73 patients (74%), type 2 in 15 (15%), type 3 in 6 (6%) and type 4 in 1 (1%). Line probe assay further subdivided type 1 into 1a (n = 35) and type 1b (n = 37) and type 2 into type 2a (n = 6) and 2b (n = 9). The most prevalent genotype observed in indian population was 1b (43.4%) followed by 3b (30.2%). The other genotype 1a was observed in 16.6% of patients followed by 3a observed in 3.4%of the patients.[22] Suou, et al.[23] carried out a genotypic analysis of HCV in Japanese population. They found genotypes la-2b in 453 of 461 patients with chronic hepatitis C, from whom 349 (76%) patients were identified as genotype lb and only one patient had genotype la.

We can observe that our results are compatible with American and Indian population, specifically in genotype 1b. This is the first study performed in Mexico collecting representative samples from nearly the entire Republic and recruiting the highest number of cases, finding no difference in genotype prevalence when geographic areas are analyzed, thus suggesting that distribution throughout the country is very similar. Thus, we conclude that the most frequent genotype in Mexico is 1b, followed by 1a, and with 1b/1a in third place. A total of 70% has genotype 1 and 30%, genotype non-1. Genotyping is recommended prior to beginning treatment with pegylated interferon plus ribavirin; thus, dose and therapy duration may be planned for each patient.

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APPENDIX 1

This trial was performed by The Mexican Study Group of Pegasys, which includes

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