Chronic hepatitis C

Genotypes and response to anti-viral therapy among Saudi patients

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ABSTRACT

Objectives: The aim of this study is to compare the response of hepatitis C virus (HCV) genotype 4 with other genotypes to anti-viral treatment among Saudi patients in a prospective randomized trial.

Methods: The study was conducted in the Department of Hepatobiliary Sciences at King Abdul-Aziz Medical City, King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia from March 1997 to January 2000. Sixty-two patients (33 males and 29 females) aged ≥18 with chronic hepatitis C not treated previously were tested for HCV genotype and randomly assigned to receive interferon (IFN) alfa 2b 3 million units 3 times per week alone or in combination with ribavirin 1000-1200mg orally per day for 48 weeks. All patients were monitored for safety and efficacy of the therapy at 4 week intervals during treatment and followed up for at least 24 weeks after completion of treatment. The primary end point was loss of detectable HCV-RNA 24 weeks after treatment completion, defined as sustained virological response (SVR).

Results: Hepatitis C virus genotype 4 was seen among (64.5%) HCV Saudi patients. Hepatitis C virus genotype 1 was the next most common (30.6%). A SVR of 42.8% (9 out of 21) was seen in HCV genotype 4 and 40% (4 out of 10) among other HCV genotypes with combination therapy of IFN and ribavirin ($p>0.1$). With IFN alone the sustained response rate was 15.7% for genotype 4 and 16.6% for other genotypes mainly genotype 1 ($p>0.1$)

Conclusion: We concluded that HCV genotype 4 is the most prevalent genotype among HCV infected Saudi patients. Genotype 1 was the next most common while genotypes 2, 3 and 5 were least prevalent. There is no statistically significant difference in response rate of patients with HCV genotype 4 to either IFN alone or IFN plus ribavirin when compared with genotype 1 of HCV.

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Chronic infection with hepatitis C virus (HCV) affects 170 million individuals worldwide.[1] It is estimated that nearly 5 million people in Europe and 4 million in United States of America are affected.[2] Twenty to thirty percent of these individuals will eventually develop cirrhosis and its complications.[3,4] Infection with HCV is the leading cause of chronic liver disease and the most common indication for liver transplantation.[5] In Saudi Arabia, HCV infection prevalence is approximately

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1.5-2.5%, an important healthcare problem with high morbidity and mortality.[6-7] Until 1995 interferon (IFN) alfa monotherapy was the only antiviral therapy available for patients with chronic hepatitis C with a low (15-20%) response rate after treatment for 48 weeks.[8,9] Since then several studies have shown encouraging results with virological response rate up to 60% with a combination therapy of IFN and ribavirin.[10,11] However, most of the patients in these studies have been non-4 HCV genotype.[1-3] In the Middle East, HCV genotype 4 is the most prevalent genotype ranging from 60-90% while genotype 4 is rare in North America and Europe.[12-14] Hepatitis C virus genotype 4 has been considered to be difficult to treat and poorly responsive to conventional IFN based therapy.[15] The efficacy of antiviral therapy in patients with HCV genotype 4 in comparison with other less common genotypes in Middle East is unclear.

The aim of our study was to compare the response of patients of HCV genotype 4 with other genotypes to anti-viral treatment among Saudi patients in a prospective randomized trial.

Methods. The study was conducted in the Department of Hepatobiliary Sciences and Liver Transplantation, King Abdul-Aziz Medical City, King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia. Patients enrollment began in March 1997 and trial was completed in January 2000. Saudi adult patients aged ≥18 were included in the study provided they were hepatitis C virus-ribonucleic acid (HCV-RNA) positive by Chiron Quantiplex branched DNA, a liver biopsy performed within one year was consistent with diagnosis of chronic hepatitis C and had elevated serum alanine aminotransferase (ALT) levels for previous 6 months. Other criteria essential for inclusion were a compensated liver disease with normal bilirubin, serum albumin, coagulation profile and normal serum alpha-fetoprotein levels. A negative human immunodeficiency virus (HIV) and hepatitis B surface antigen and a normal hematological profile were essential. Patients with decompensated cirrhosis, co-infection with hepatitis B or HIV and other liver diseases, namely autoimmune, alcoholic, drug induced, metabolic or obesity related, were excluded. Similarly, patients with psychiatric disorders, seizure disorders, poorly controlled diabetes mellitus, autoimmune disorders, significant cardiopulmonary diseases and previous organ transplant were not included. Patients with prior treatment with IFN or ribavirin or current therapy with immunomodulator drugs and those unable to practice effective contraception were also excluded. Sixty-two eligible patients were randomly assigned to the 2 treatment groups with intention to treat: a) Group A - recombinant IFN alfa-2b (Intron A, Schering Plough) plus ribavirin (virazole ICN pharmaceuticals for 48 weeks). b) Group B - IFN alfa-2b (Intron A) alone for 48 weeks. All patients received Intron A 3 million units (MU) subcutaneously 3 times a week and ribavirin was given orally 1,000 mg/day (body weight <75kg) and 1200 mg/day (body weight >75 kg) in 2 divided doses. The patients were regularly followed up for safety and efficacy of therapy in outpatient clinic every 4 weeks during treatment and at 12 and 24 weeks after completion of therapy. Biochemical and hematological tests were performed at each visit. Hepatitis C virus-RNA levels were determined in all patients pretreatment, during treatment at 12 weeks and 24 weeks after completion of treatment. Hepatitis C virus-RNA levels were measured by branched DNA (bDNA) assay at Pasteur cerba-laboratory Paris with sensitivity of 0.2 x 10e6 equivalent-genomes/ml. Pretreatment liver biopsy was performed in all patients and were analyzed by a single pathologist. Hepatic inflammatory activity was assessed by modified Knodell histological activity index (HAI) and expressed as the score of hepatic activity index (HAI score). Hepatitis C virus genotyping was performed in all patients by polymerase chain reaction (PCR) and line probe assay (LiPA) hybridization. Side effects of therapy were grouped into early and late, and graded as mild, moderate and severe in nature. The primary efficacy end point for this trial was a sustained virological response (SVR), defined as absence of serum HCV-RNA 24 weeks after treatment completion. Secondary end point was the normalization of serum ALT levels; the biochemical response. Patients who had virological and biochemical response maintained at week 24 after treatment completion were labeled sustained responders. Patients with failure to normalize serum ALT and with positive HCV-RNA at 6 months during therapy were labeled treatment failure, treatment was suspended and labeled as non-responders. Patients with initial biochemical and virological response followed by a relapse in one or more of these parameters within 6 months of completion of therapy or during therapy were defined as relapsers.

The baseline of patient's characteristics and variables of the 2 treatment groups were similar and are given in **Table 1**. None of the variables was significantly different between the 2 groups.

Frequency, statistical analysis and students t-test were applied to analyze patient's characteristics and variables and results of treatment among the 2 groups of patients.

Results. At 24 weeks after the end of treatment, the SVR rate was significantly higher (13/31; 42%) among patients who received IFN and ribavirin for 48 weeks than among those who received IFN alone for 48 weeks (5/31; 16%) $p<0.05$. The overall

Table 1 - Patient's characteristics and variables.

Characteristics and variables	Interferon alone (N=31)	Interferon and Ribavirin (N=31)
Gender		
Male	16	17
Female	15	14
Age range	22-64	28-68
Mean age (years)	(45.2)	(49.3)
Body weight (kg)	77.5 ± 15.2	73.4 ± 17.2
Serum ALT	1.19 ± 0.17	1.67 ± 0.07
HAI Score	7.19 ± 2.9	7.3 ± 3.5
Genotypes		
1	9	10
4	19	21
3a	2	
5a	1	

ALT - alanine aminotransferase, HAI - histological activity index

Table 2 - Virological and biochemical response 24 weeks after the end of treatment.

Response rate	IFN alone N=31 n (%)	IFN plus Ribavirin N=31 n (%)
Virological		
Patients with sustained response	5 (16.1)	13 (41.9)
Patients with no response	22 (71)	13 (41.9)
Patients who relapsed	4 (12.9)	5 (16.1)
Patients with treatment failure	26 (83.9)	18 (58.1)
Biochemical		
Patients with response at the end of follow-up	12 (38.7)	20 (64.5)

IFN - inteferon

Table 3 - Genotypes and sustained response rate.

Genotypes	N of patients	IFN alone number/total number of patients n (%)	IFN plus Ribavirin number/total number of patients n (%)
Genotype 1, 3 and 5	22	2/12 (16.6)	4/10 (40)
Genotype 4	40	3/19 (15.7)*	9/21 (42.8)*

*not significant, IFN - inteferon

treatment failure rate was higher (83.8%) in patients who received IFN monotherapy in comparison to patients who received combination of IFN and ribavirin (58.1%) (**Table 2**).

The majority of our patients (40/62; 64.5%) were genotype 4 and genotype 1 (19/62; 30.6%). There was no statistically significant difference in response rate of patients with HCV genotype 4 to either IFN alone or IFN plus ribavirin when compared with genotype 1 of HCV. When treated with IFN alone SVR rate was 15.7% for genotype 4 and 16.6% for other genotypes (not significant). With IFN and ribavirin combination, SVR was achieved in 42.8% of HCV genotype 4 and 40% of patients with other genotypes, mainly genotype 1 (**Table 3**).

The other pre-treatment patient variables of age, gender, body weight, serum ALT levels and HAI score were similar among the 2 patient groups and did not seem to affect the treatment outcome. The biochemical response rate at end of follow-up was higher (64.5%) in patients treated with combination of IFN and ribavirin than in patients treated with IFN alone (38.7%) ($p<0.05$). Normalization of serum ALT was observed in all patients who had SVR. However, 22.6% of patients in both groups with sustained biochemical response had persistently detectable HCV-RNA.

Mild and early onset adverse effects including flu and such as symptoms including cough, headaches, myalgias and arthralgias were observed in 24 out of 31 (77.4%), which required only symptomatic treatment. Patients receiving combination of IFN and ribavirin had a similar rate (26/31; 83.8%) of adverse effects. Twelve patients (38.7%) developed hemolysis resulting in decrease in hemoglobin. However, hemoglobin stabilized after dose reduction of ribavirin and no patient required blood transfusion. Severe depression developed in one patient necessitating discontinuation of treatment of IFN and ribavirin. Three patients had skin rash and one had a significant alopecia.

Discussion. This randomized trial has shown that genotype 4 is the most prevalent genotype (64.5%) among Saudi population. Our results showed a low response rate (15.7%-16.6%) with IFN alone regardless of viral genotype which was similar to previously observed response rates of 15-20% with this regimen.[8,9] There was more than a 2-fold increase in response rate with combination regimen when compared with IFN alone regardless of genotype of HCV. There were no statistically significant difference in response rates between genotype 4 and other genotypes treated with combination of IFN and ribavirin. However most, (19/62; 30.6%) of our patients were genotype 1. Sustained virological response in patients with

genotype 4 HCV was as high as in those patients with genotype 1. Our results are consistent with those of recently concluded study among Saudi patients.[16,17]

In summary, genotype 4 is the most common in our study group population and response rate is reasonably good at least 2-fold (42.8% versus 15.7%) higher with combination treatment. This response rate of HCV genotype 4 is no different when compared with patients with genotype 1. Hepatitis C virus genotype 4 should not be considered as difficult to treat or poorly responsive genotype

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