

Response to Interferon Therapy in HCV Patients in Private Clinic

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ABSTRACT

Aim: To determine response of HCV patients to conventional interferon therapy and also identify genotype in non-responders.

Methods: A prospective study of patients presenting with hepatitis C infection from Jan 2008 to Dec 2012 was performed. 716 patients were enrolled, 513 patients completed the study. They were treated with a combination of interferon alpha 2b (3 MU subcutaneously three injections weekly) and ribavirin (800–1200 mg orally daily in divided doses). Treatment was administered for 24 weeks, end of the treatment response (ETR) were recorded and pts were followed for additional 6-24 months thereafter.

Results: Out of 513 patients who completed study, 78% patients were between 21 to 50 years of age. Commonest clinical feature were anemia 38.6%, generalized body aches 31.7%, and leg pains 23%. ALT was minimally high (31% of patients). 67% responded to treatment. Most common genotype found was 3a (53.6%) and 3b (12.3%) along with untypeable 21% in non-responders and relapses.

Conclusion: The response rate to conventional interferon therapy was 67%. Majority of patients who relapsed were having genotype 3a or untypeable genotypes suggesting the probability of genetic mutations.

Keywords: Inteferon therapy, HCV, private clinic

INTRODUCTION

Hepatitis C is a common public health problem and it is an important cause of chronic liver disease. After acute HCV infection, up to 85% of patients develop chronic hepatitis C followed by cirrhosis (10-20%) and 1-5% may develop hepato-cellular carcinoma in 20-30 years time^{1,2}.

Overall, HCV causes 20% of acute hepatitis cases, 70% of all chronic hepatitis cases, 40% of all cirrhosis of liver, 60% of hepato-cellular carcinomas and 30% of liver transplants, especially in Europe³. World Health Organization (WHO) estimates up to 3% of the world's population to be infected with HCV and worldwide there are more than 170 million chronic carriers of HCV⁴.

Hepatitis C Virus (HCV) is classified into different genotypes depending on nucleotide sequence variability. Currently, HCV is divided into six major genotypes (1-6) based on genetic sequence, and then subdivided into over 50 alphabetically designated subtypes⁵.

HCV subtypes 1a and 1b are the most common genotypes in the United States⁶. These subtypes also is responsible for up to 73% of cases of HCV

infection¹⁰. Although HCV subtypes 2a and 2b are relatively common in North America, Europe, and Japan, subtype 2c is found commonly in northern Italy. HCV genotype 3a is particularly prevalent in intravenous drug abusers in Europe and the United States¹¹. HCV genotype 4 appears to be prevalent in North Africa and the Middle East^{12,13}, and genotypes 5 and 6 seem to be confined to South Africa and Hong Kong, respectively^{14,15}. HCV genotypes 7, 8, and 9 have been identified only in Vietnamese patients¹⁶, and genotypes 10 and 11 were identified in patients from Indonesia¹⁷. HCV genotype 2 and 3 is the most frequent genotype found in Pakistan¹⁸.

MATERIAL AND METHOD

This prospective study was conducted in a private clinic at Dabgari Garden, Peshawar between Jan 2008 to Dec 2012 and included consecutive patients diagnosed with hepatitis C and HCV RNA positive. Detailed clinical history and examination was done and findings were recorded. The routine investigation of the patient including complete blood count, serum alanine aminotransferase levels were done along with ultrasound abdomen if indicated. Real-time PCR (RT-PCR) was done mostly in a single reference laboratory for determination of HCV RNA. Informed consent was obtained from all the participants. Eligible patients were assigned to receive subcutaneous injection of 3MIU standard interferon α -2b thrice weekly and ribavirin 10.6mg/kg/d mg/day in two or three divided dosages for 24 weeks. HCV RNA was done again at the end of treatment to find out treatment response.

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RESULTS

A total of 716 patients were included in the study. These individuals belonged to various districts of KPK along with afghan refugees (Fig. 1). Out of the total 716, 316 were males while 400 were female (table 4). All the individuals were categorized into six age groups (Table 1). After Peshawar 24%, afghan refugees 18.5% and Fata 18%, most of the patient presented from districts Mardan, Malakand, Hangu, Charsadda and Kohat. The majority of the patients (78%) were between 21 to 50 years of age. The common presenting clinical features were anemia 38.6%, generalized body aches 31.7%, and leg pains 23%. ALT was minimally high in 31% of the patients. HCV antibody was detected in patient before treatment by Elisa followed by HCV RNA detection. Five hundred and three (71.6%) patients completed the treatment while rest of the patients were lost to follow up. 67.2% who completed treatment have responded to it while 28.9% did not achieve complete response (Table 4).

Table 1: Age range of HCV patients

Age range	no.	%
<20	54	6.1
21-30	261	28.5
31-40	235	25.3
41-50	251	24.5
51-60	111	14.1
61-70	5	1.1

Table 2: Pre-treatment common clinical features of HCV patients

Pre-treatment Clinical Feature	No.	%
Anemia	277	38.6
Generalized Body Aches	227	31.7
Leg Pain	164	23.0
Hepatomegaly	36	5.0
Splenomegaly	12	1.7

Table 3: Variable associated with HCV patients before and after treatment

Variable	No.	%
Male	316	44.2
Female	400	55.8
Pre treatment Hb		
Normal	458	64
Low	258	36
Pre-treatment Platelets		
Normal	516	72
Low	200	28
Pre-treatment ALT		
Minimal high	500	69.9
Moderately high	216	30.1

Table 4: Treatment Response of HCV patients

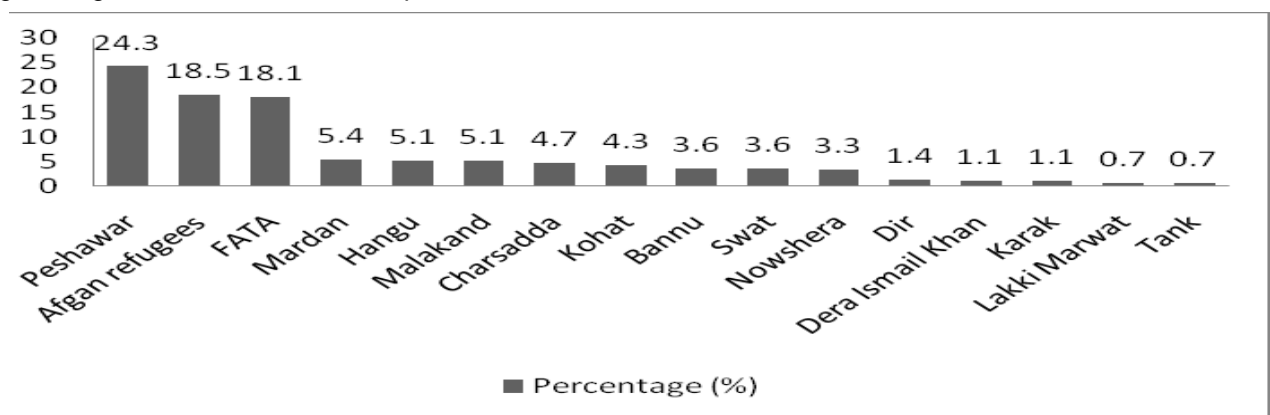
Response	No.	%
Total patients enrolled	716	-
Patients who completed treatment	513	71.6%
Patients who lost to follow up	203	28.4%
Patients responded to treatment	345	67.2%
Patients not responded to treatment	148	28.9%

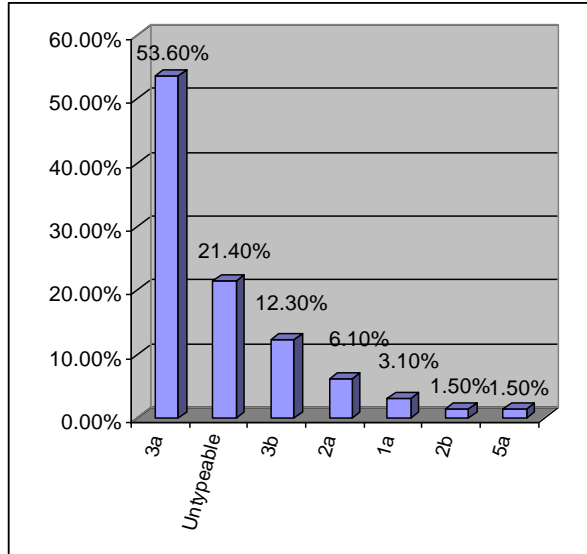
Table 5: Relapses at 06-months/12-months/18-months/24-months

Status	At 6 month EOT		Post 6 month EOT		Post 12 month EOT		Post 18 month EOT		Post 24 month EOT	
	No.	%	No.	%	No.	%	No.	%	No.	%
Responders	255	69.96	45	71.43	23	50.00	15	66.67	41	69.23
Non-Responder	110	30.04	11	16.67	8	16.67	2	6.67	6	10.26
Relapses*	-	-	8	11.90	15	33.33	6	26.67	12	20.51
Total	365		63		45		23		59	

*detected for first time after treatment completion

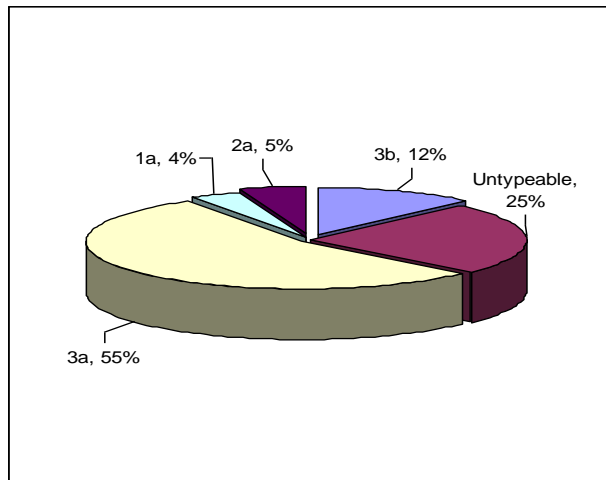
Fig. 1: Regional Distribution of HCV patients





*Number of patients in which genotype was checked is 98

Fig. 3: Distribution of different HCV genotypes in non-responders*



*Total number of non-responder patients in which genotype was checked is 77

DISCUSSION

Hepatitis C is rapidly rising as a major health problem in developing countries including Pakistan^{19,20}. Conventional interferon (C-INF) therapy is used for HCV treatment in poor countries because of financial reasons and Pakistan Society of Gastroenterology and GI Endoscopy also recommend the use of C-INF therapy for HCV genotype 3 in Pakistan^{21,22}. The currently recommended treatment regimen of chronic HCV infection is the combination of a pegylated interferon alfa and ribavirin based on three randomized clinical trials that demonstrated the superiority of this combination treatment over standard interferon alfa and ribavirin^{23,24,25}. But in

under developed and developing countries including Pakistan, pegylated interferon therapy is beyond the reach of common poor patients^{21,26}. Retreatment with peginterferon plus ribavirin can be considered for non-responders or relapsers who have previously been treated with non-pegylated interferon with or without ribavirin, or with peginterferon monotherapy, particularly if they have bridging fibrosis or cirrhosis²⁷.

This study was conducted using conventional interferon plus ribavirin in standard doses for six months. Patients were followed every month for development of drug side effects and their routine blood counts and platelets counts, serum ALT and blood sugars were checked. 345 patients (67%) responded to the treatment after its completion and became PCR negative at six months; remaining 148 patients (23%) did not responded to treatment and were labeled non-responders. Our study shows 67% response rate to therapy which is less than response rate found in other studies, 70-80%²⁸ but there are studies done in Pakistan which shows a treatment response rate of 67%²⁹.

The study revealed that middle aged and elderly people of different districts (in the age groups of 20-50 years) had active HCV infection. The lesser number of young people with HCV infection may indicate better awareness about HCV infection, less exposure to some of the risk factors causing HCV including major/dental surgery, blood transfusion or intravenous injections. These findings were similar to other studies which conducted HCV prevalence in relation to age groups^{30,31}.

Female patients were more affected by HCV as compared to their male counterparts i.e. 55.5% vs 45.5%. Female patients are more exposed to injudicious and unsafe use of injection for minor illnesses, mostly on their demand. HCV infection was also more commonly reported in female by other studies including Rauf et al i.e., 68% vs. 32%³², and by Mahmood et al, i.e. 55% vs 45%³³.

Genotyping was done mostly on non-responders and it revealed genotype 3a as the predominant genotype in non-responders. Analysis of the data showed that genotype 3a is the predominant genotype circulating in patients with chronic hepatitis C. These findings verified results of the earlier studies from Pakistan^{34,35,36} which have concluded that genotype 3a is the most prevalent HCV genotype in Pakistan. Similarly in India, the predominant HCV genotype is 3a^{37,38}.

Our finding regarding distribution of the genotype seems to be similar to the genotype pattern reported from other South Asian country such as Nepal³⁹ but different from those in Far-east Asian countries such as Japan⁴⁰, Thailand⁴¹ and Vietnam

where genotype 1 is the major HCV genotype circulating in their populations.

Our findings confirm previously reported work that shows better response to INF-alpha treatment in patient with HCV genotypes 2 and 3^{41,42,43}.

CONCLUSION

The response rate to conventional interferon therapy was 67% which is comparable to other studies. Majority of the patients who relapsed were having genotype 3a or untypeable genotypes which suggests the probability of genetic mutations. Most of the patients having HCV RNA positive had normal ALT or minimally high ALT, so monitoring should not be dependent on ALT estimation in identifying RNA positive patients, and patients should be followed up with RNA detection rather than ALT estimation.

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