



INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH



FACTORS REFRACTORY TO CONVENTIONAL INTERFERON BASED THERAPY IN CHRONIC HEPATITIS C

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ARTICLE INFO

Article history

Received 17/01/2017

Available online

31/01/2017

Keywords

HCV,
Non Responders,
Break Through Responders,
Relapsers.

ABSTRACT

OBJECTIVE: To determine the factors in patients suffering from chronic HCV, refractory to conventional interferon therapy. **MATERIAL & METHODS:** This descriptive case series study was conducted at Out Patient's Department of Hepatitis Control Program at Medical Unit IV, LUMHS Hospital Jamshoro from June 2013 to December 2013. Based on Inclusion and Exclusion criteria, a total of Eighty (80) patients with the established diagnosis of chronic Hepatitis 'C' were recruited by Non-probability consecutive sampling technique after obtaining a well informed and written consent. Socio-demographic data and history of alcohol addiction (>50gm/day), examination of weight and height to calculate BMI and Investigations including: HCV RNA by PCR and Liver Biopsy were recorded on a semi-structured proforma specifically designed for the study. **RESULTS:** A total of eighty (80) patients were included in the study who are refractory to conventional interferon therapy from which 49(61.20%) were male and 39(38.80%) were female. The mean age and SD were 40.70+6.37 years. On the basis of refractory category 57(71.2%) were non responders, 06(7.5%) were break through responders and 17(21.2%) were relapsers. On the BMI distribution mostly patients 55(68.80%) were with >30 and 25(31.20%) cases were between 25-30. Grade II steatosis was found in the mostly the cases 31(38.8%), Grade I steatosis was also commonest in 30(37.5%) of the cases, while 15(18.8%) patients were found with Grade O steatosis and only 4(5%) cases were documented with Grade III steatosis. From total number only 25(31.25%) had history of alcohol addiction and from 25, 15(80.0%) patients were consuming >50 gm/day of alcohol and 05(20.0%) <50 gram/day. 56(70%) patients were noted with VL >8, 00000 IU/ml while 24(30%) patients were with viral load of <8, 00000 IU/ml. F2 was found commonest in the patients 43(53.8%), while F1, F3, F0 and F4 were noted with frequency/percentage of 21(26.2%), 08(10.0%), 06(7.5%), 02(2.5%) respectively. **CONCLUSION:** This study had concluded that there were a number of factors responsible for refractory treatment with conventional interferon based therapy in the cases of chronic HCV infection. Gender (male), age (>40 years), (BMI>30kg/m²), elevation of grade of steatosis, stage of fibrosis and high viral load are highly responsible factors. Therefore, it is recommended that all these common factors should be kept in mind during interferon therapy and future advance multidisciplinary studies will be conducted at various health care centers to compile the data and observe the other factors responsible for refractory treatment as far as HCV treatment is concerned.

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Please cite this article in press as **Dr. Sunil Dat Maheshwari et al. Factors Refractory to Conventional Interferon Based Therapy in Chronic Hepatitis C. Indo American Journal of Pharmaceutical Research. 2017;7(01).**

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INTRODUCTION

Hepatitis 'C' is a rising health problem, about 180 million populations is suffering from Hepatitis 'C' worldwide [1]. No doubt that developing countries are not so far in sharing the huge global burden of Hepatitis 'C'. The prevalence of Hepatitis C is 4.5-8% in Pakistan affecting nearly 10 million peoples throughout country. [2,3] About 66% of Pakistan peoples are belongs to rural areas, where the rate of Hepatitis 'C' is much higher as compared to urban areas. [3] The natural history of Hepatitis 'C' is variable, [1] according to an estimate Hepatitis C Virus leads to Chronic Hepatitis in 50-80% of infected patients, [2] 15-30% cases of Chronic Hepatitis develop Cirrhosis and about 1-3% of Cirrhotic patients develop HCC. [1] WHO have estimated 785,000 and 308,000 deaths annually by Hepatitis C related Cirrhosis and Liver Cancer respectively. [2,3]

The therapy have evolve to Interferon (3 MIU thrice weekly) plus Ribavirin (800-1200mg/ day) and it becomes a standard therapy with 38-43% sustained virologic response. [4] Peginterferon and Ribavirin are used as a regular therapy. [4] The response to standard treatment is different in different patients; more than 60% of patients either shows no response or relapse after the completion of therapy. [5,6] The factors responsible for the failure of therapy are:

GENDER: Estrogen enhances the response of therapy and because of this Female responds better than Male. [7]

AGE: Elder individuals (Age > 39 yrs.) shows poor response to therapy as compared to young age population due to level of immunity and stage of liver disease. [7,8]

OBESITY: Increased Body Fat Mass (BMI > 25) and Hepatic Steatosis are factors responsible for non-response of therapy in obese patients. Both factor decreases the bioavailability of Interferon and Ribavirin, decreases the immune response to Hepatitis 'C' Virus and increases the Fibrosis. [9,10]

ALCOHOL: Alcohol directly inhibits the activated signals of interferon alpha, beta and gamma in the hepatocytes via activation of p42/44 MAP kinase and protein kinase C. [11]

GRADE OF FIBROSIS: The intrahepatic changes due to fibrosis or it's progression to Cirrhosis leads to poor response to therapy. [12,13]

VIREMIA: HCV RNA level (> 8,000,000 IU/ml) is responsible for non-response of therapy. HCV mediated cellular immune responses and antiviral proteins such as PKR effects the actions of therapy. [14-18]

The proposed of this study was to determine the factors responsible for failure of conventional interferon based treatment of patients with chronic HCV in our population, which will help in reduce the burden by suggesting alternative treatment options with good efficacy and preventing them from adverse effects of low efficacy treatment as early stratification and management of those factors can prevent the patient to acquire advance liver disease.

PATIENTS AND METHODS

This descriptive case series of six months was conducted at out Patient's Department of Hepatitis Control Program at Medical Unit III, LUH Jamshoro. The inclusion criteria of the study were hepatitis C 'Non-Responders', Breakthrough Responders and 'Relapsers' (see operational definition) to conventional interferon therapy taken for six months (24 weeks), while the exclusion criteria were; Patient's with decompensated liver cirrhosis, hepatoma and other co-morbidities like diabetes mellitus. The source of this study was the patients attending Out Patients Department of Hepatitis Control Program at Medical Unit III, Liaquat University Hospital Jamshoro. On the basis of Inclusion and Exclusion criteria, the patients were selected after the informed consent and subjected to, Specific History like Name, Age, Gender, Address, Contact Number, history of alcohol addiction (> 50 gm/day), examination of weight and height to calculate BMI() and Investigations including: HCV RNA by PCR and Liver Biopsy. To prepare the patient for Liver biopsy some pre-requisite investigations were also be carried out. All the investigations were sent to Diagnostic and Research Laboratory, LUH, and Ultrasound was from Department of Radiology, LUH Jamshoro. The Liver biopsy samples were sent to Histopathology Department of LUMHS Jamshoro. All the information specifically designed proforma. SPSS version 16 was used for data analysis.

RESULTS

Total 80 patients were included in the study from which male were found in the majority 49 (61.20%) as compared to the female that were 39 (38.80%). FIG: 1.

Mean age and SD was 40.70 ± 6.37 years in this study with the range of 23-55 years. TABLE: 1.

Mosly patients were from urban areas 45 (56.20%) and from rural areas were 35 (43.80%). FIG: 2.

According to refractory category, non responder patients were noted in the majority 57 (71.2%), while break through responders and relapsers were found 6 (7.5%) and 17 (21.2%) respectively. TABLE: 2.

On the BMI distribution, mosly patients 55 (68.80%) were with $> 30 \text{ kg/m}^2$ BMI and 25 (31.20%) cases were between 25-30 kg/m^2 . TABLE: 3.

From total 80 number, only 25 (31.25%) had history of alcohol addiction and from 25, 15 (80.0%) patients were high alcohol consumers (> 50 gm/day of alcohol) and 05 (20.0%) were low alcohol consumers (< 50 gram/day of alcohol). TABLE: 3

This study had used the grades of steatosis which are divided as: GRADE 0: No Steatosis (< 1% total Hepatocytes), GRADE I: Mild Steatosis (Between 1% - 30% of Hepatocytes), GRADE II: Moderate Steatosis (Between 30% - 60% of Hepatocytes) and GRADE III: Severe Steatosis (Between > 60% of Hepatocytes) ²⁰. Grade II (Moderate steatosis) was found in the mosly the cases 31 (38.8%), Grade I (Mild steatosis) was also commonest n in 30 (37.5%) of the cases, while 15 (18.8%) patients were found with Grade O (No steatosis) and only 4 (5%) cases were documented with Grade III (severe steatosis). TABLE: 3.

According to Metavir Staging System fibrosis is classified as, STAGE 0(F0):No Fibrosis, STAGE I (F1):Fibrous Portal Expansion, STAGE II (F2):Fibrous bridging Fibrosis, STAGE III (F3): BF with Lobular distortion and STAGEIV (F4):Cirrhosis. F2stage was found commonest n in the patients 43(53.8%), while F1, F3, F0and F4 were noted with frequency/ percentage of 21(26.2%), 08(10.0%), 06(7.5%), 02(2.5%) respectively. TABLE: 3. Mostly patients 56(70%) patients were noted with VL >8, 00000 IU/ml while 24(30%) patients were with viral load of <8, 00000 IU/ml. TABLE: 3.

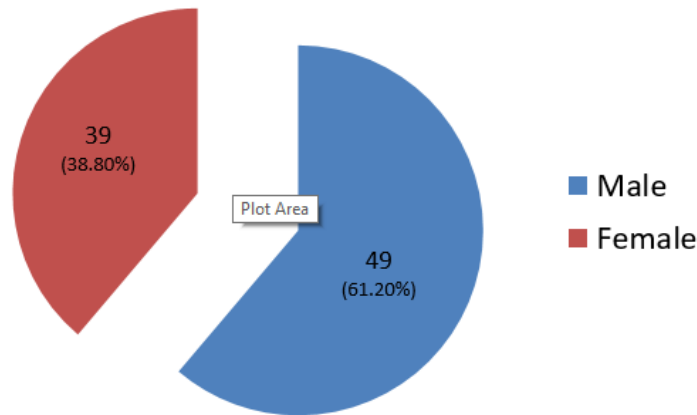


FIGURE: 1. GENDER DISTRIBUTION. N=80

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TABLE: 1. AGE OF THE PATIENTS. N= 80.

AGE	
Mean	40.70 years
SD	6.37
Range	23-55 years

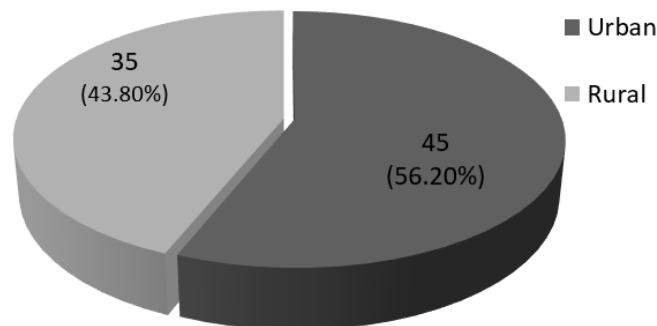


FIGURE: 2. RESIDENTIAL DISTRIBUTION OF THE PATIENTS. N=80

FIGURE: 2. RESIDENTIAL DISTRIBUTION OF THE PATIENTS. N=80.

TABLE:2. REFRACTORY CATEGORY OF THE PATIENTS. N=80.

CATEGORY	FREQUENCY	%
Non Responders	57	71.2
Break through Responders	06	07.5
Relapsers	17	21.2

TABLE:3. FREQUENCY OF FACTORS REFRACTORY TO THERAPY IN PATIENTS. N=80.

Factors	Frequency	Percentage
BMI		
<25	00	00
25-30	25	31.2
>30	55	68.8
Alcohol Consumption		
Low alcohol consumption	05	20
High alcohol consumption	20	80
Steatosis		
Grade 0	15	18.8
Grade I	30	37.5
Grade II	31	38.8
Grade III	04	05
Fibrosis		
F 0	06	7.5
F 1	21	26.2
F 2	43	53.8
F 3	08	10
F 4	02	2.5
Viral Load		
>800,000 IU/ml	56	70
<800,000 IU/ml	24	30

DISCUSSION

Day by day Hepatitis C is increasing worldwide and its refractory status of treatment to antiviral therapy is very common. [19] With the advent of anti-viral therapies, more and more peoples are seeking treatment. Non-response and relapse are an emerging issue with the use of conventional regimen. Therefore, it is important to study the effect of different causes of non-response and relapse.

In this study, male was found more with refractory to treatment that is 61.20% as compared to the female that is 38.80% and mean age was 40.70±6.37 years. Shafi MS et al, [20] reported that male were in the majority as compared to female in the list of refractory treatment compared to former literature [21].

This study had divided the patients on the basis of refractory category and non- responders were found in the majority 71.2%, while break through responders and relapsers were s data is dissimilar from studies. Qureshi S et al [22], mentioned 18.4% were non responders and 27.7% were relapsers. Shaikh S et al [23], reported frequency of relapsers were 42.6%, breakthrough responders 20.5% and non-responders were 36.6%.

According to BMI distribution in this study, no patient found with BMI<25, 31.20% cases were between 25-30 while mostly patients 68.80% were with >30 which is nearly same result as mentioned in the study of Shaikh S et al [23], that showed 62.4% with > 30 kg/m² and < 30 kg/m² in 37.6% patients. Hickman I.J et al [24] stated that obesity is associated with a reduced response to treatment as well as increased steatosis and fibrosis.

Caroline Le Lan et al [25], discussed the alcohol consumption and mentioned that 65% patients were abstinent, 25% patients with low consumption of alcohol and 20% patients were with extra use alcohol during treatment. While in this study same data recorded, according to the history of alcohol, 68% were abstinent, 25% were noted with low alcohol utilization and 7% cases were found with unnecessary alcohol uses. Singal A Ket al.[26] concluded that utilization of Alcohol linked to reduce standard interferon response.

Genotype 3 not linked to lower sustained response [27]. In this series Grade II or moderate steatosis was found in the mostly the cases that is 38.8%, grade I or mild steatosis was also commonest n in 37.5% of the cases, while 18.8% patients were found grade O or No steatosis and only 5% cases were documented with grade III or severe steatosis. L Caste´ra et al [28] also divided the Steatosis in the same way but differs in data and reported, 55.0% of cases were with grade I or mild steatosis, grade II or moderate in 21.2%, and grade III or severe in 23.8%. The data by P. Fabris, et al, [29] reports same result as this study. Grade II or moderate steatosis was found in 40%, 35% grade I or mild steatosis and cases in grade O and grade III were 15% and 10% respectively.

Hepatic fibrosis is the in response to stimuli in acute or chronic liver disease [30,31]. The present series described that Stage II fibrosis was found commonest n in 53.8% of patients, while Stage I fibrosis, Stage III fibrosis and Stage O fibrosis and Stage 4 fibrosis or Cirrhosis were noted with frequency/ percentage of 26.2%, 10.0%, 7.5%, 2.5% respectively. Shaikh S et al [23], described in his study that fibrosis stage 2 was present in 65.5%, stage 3 in 25.6% and fibrosis stage 4 was present in 8.9% patients. Everson et al [32] mentioned that the presence of advanced fibrosis and cirrhosis is a major independent predictor of nonresponse to antiviral therapy. Poynard et al[33]. reported that cases having chronic HCV undergoing IFN treatment, the presence of no fibrosis or fibrosis limited to the portal tract alone was independently associated with SVR on multivariate analysis.

Majority (70%) of patients were found with VL >8, 00000 IU/ml while only 30% patients were with viral load of <8, 00000 IU/ml compared with several former studies [34-36].

CONCLUSION

This study had concluded that there were several factors responsible for refractory treatment with conventional interferon based therapy in the cases of chronic HCV infection. Gender (male), age (>40 years), (BMI>30kg/m²), elevation of grade of steatosis, stage of fibrosis and high viral load are highly responsible factors. This study had also look and found a strong association between the BMI, Steatosis, Fibrosis and non response, break through response and relapse. However, our understanding of the variable response in different patients is still unclear and more research is required to further elucidate the complex interactions between the chronic HCV condition and its response to conventional interferon therapy.

Therefore, it is recommended that all these common factors should be kept in mind during interferone therapy and future advance multidisciplinary studies will be conducted at various health care centers to compile the data and observe the other factors responsible for refractory treatment as far as HCV treatment is concerned.

ABBREVIATION:

BMI	Body mass index
F	Fibrosis
HCV	Hepatitis C virus
INF	Interferon
IU	International unit
LUH	Liaquat University Hospital
LUMHS	Liaquat University of Medical and Health Sciences
MAP	mitogen-activated protein kinase
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
SD	Standard Deviation
SPSS	Statistical Package for the Social Science.
VL	Viral load

ACKNOWLEDGEMENT

Mr. Muhammad Jan for computer assistance and record maintainance.

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