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Risk Factors for Treatment Failure with Oral Antivirals in HCV

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ABSTRACT

Introduction: Chronic hepatitis C virus (HCV) infection is one of the major cause of cirrhosis of liver and leads to significant morbidity and mortality. In past, HCV therapy was limited to subcutaneous peg interferon plus oral ribavirin, a regimen that was generally poorly tolerated and provided low efficacy, with cure rates below 40% for HCV genotypes 1 and 4, and below 75% for HCV genotypes 2 or 3. The availability of oral direct-acting antiviral (DAA) as treatment for chronic hepatitis C has revolutionized the field. Although current HCV therapies rarely fail to achieve viral eradication, a subset of patients experience treatment failure.

Aim: To study the risk factors associated with treatment failure with oral antiviral drugs in patients of Chronic hepatitis C.

Materials & Methods: It was a retrorospective study done at Medical Gastroenterology Department, PGIMS, Rohtak in which six years data i.e.from 01.01.2015 to 31.12.2020, pertainining to Eighty Six (86) chronic hepatitis C patients who had treatment failure i.e. SVR failure on oral antiviral drugs was analyzed.

Observations: Out of the total 86 patients, there was clear cut male predominance i.e. 54 (62.79 %) with rural background (villages) i.e.73 (84.88%). The age distribution in these 86 patients varied between 10-80 yrs of age and characterstically peak was seen in 31-40 yrs age group i.e.25 patients (29.06 %). The majority of patients had high baseline HCV viral load (> 4 lakhs I.U. /ml) i.e. 52 patients (60.46%). Out of total 86 patients, , 50 patients (58.13%) were cirrhotic, 34 patients (39.53 %) were smokers, 33 patients (38.37%) were alcoholic, 26 patients (30.23 %) had past history of surgical intervention, 9 patients (10.46 %) were diabetic, 9 patients (10.46 %) had got tattoo, 8 patients (9.30%) had history of previous blood transfusion and 13 patients (15.11%) gave history of use of alternative medications.

Results: The direct risk factors associated with development of failed SVR in HCV patients are high baseline HCV RNA viral load, cirrhosis, rural background and indirect risk factors are smoking, alcohol and Diabetes Mellitus but large scale studies in future are required to confirm the same.

KEYWORDS: Hepatitis C Virus, HCV RNA Quantitative viral load, Sustained virological response, Blood transfusion, Tattooing.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a major global health problem and has already infected 71 million patients. Highly endemic countries for HCV infection are Pakistan, Egypt, and Mongolia, where prevalence reaches 6–10% of the population **(1-3).** The chronic infection can lead to liver cirrhosis, hepatic

decompensation and hepatocellular carcinoma which are associated with high morbidity and mortality **(4-7).** In past, HCV therapy was limited to subcutaneous peg interferon plus oral ribavirin which was generally poorly tolerated and provided low efficacy, with cure rates below 40% for HCV genotypes 1 and 4, and below 75% for HCV genotypes 2 or 3 **(8)**. The availability of oral direct-acting antiviral (DAA) has revolutionized the treatment for HCV **(8).** The goal of HCV management includes prevention from getting infected with this deadly virus, early detection and treatment with antiviral treatment, so as to achieve complete viral eradication defined as undetectable HCV RNA 12 weeks after the end of antiviral treatment (sustained virological response, SVR) thus leading to reduction of its complications **(9).** The viral eradication can result in normal life expectancy in patients even in those who have already developed advanced liver fibrosis because with treatment the fibrosis gets decreased **(10)** which improves health-related quality of life **(11-14).** The DAA's are more effective, require shorter duration of treatment, have lesser side effects and can be even used in decompensated stage where Interferon (IFN) therapy is contraindicated. Although current HCV therapies rarely fail to achieve viral eradication, a subset of patients experience treatment failure. HCV relapse upon completion of therapy is by far more frequent than viral breakthrough during DAA treatment. Baseline factors associated with DAA failure include advanced liver cirrhosis, prior HCV treatment failure, high serum HCV-RNA, HCV genotypes 3 or 1a, male gender, and/or unfavorable IFNL4 polymorphisms **(15-18)**. During DAA therapy, poor drug adherence with frequent missing doses or premature drug discontinuation due to adverse events may also contribute to DAA treatment failure **(19,20).**

AIM

To study the risk factors associated with treatment failure with oral antiviral drugs in patients of Chronic hepatitis C.

MATERIALS & METHODS

It was a retrorospective study done at Medical Gastroenterology Department, PGIMS,Rohtak in which six years data i.e.from 01.01.2015 to 31.12.2020, pertainining to Eighty six (86) chronic hepatitis C patients who failed to achieve sustained virological response after 12 weeks of completion of treatment, was analyzed. As per National viral Hepatitis Control Program (NVHCP) guidelines, all non-cirrhotic patients were treated with combination of Sofosbuvir 400 mg & Daclastavir 60 mg for 12 weeks and all cirrhotic patients were treated with combination of Sofosbuvir 400 mg & Velpatasvir 100 mg for 12 weeks. The patients were labelled cirrhotic on basis of liver function test, ultrasound abdomen, fibroscan and endoscopy. The detailed laboratory investigations included HCV RNA Quantitative, anti HIV antibody, anti HCV antibody, complete blood counts, liver & renal function tests, serum electrolytes, coagulation parameters (PT, INR), blood sugar, ultrasonogram abdomen, chest x ray PA view,ascitic fluid - TLC, DLC, cultures, SAAG, Upper GI endoscopy , CECT abdomen or Triple phase CT scan of abdomen and Fibroscan.

STASTICAL ANALYSIS

Statistical analysis was performed by the SPSS program version 25.0. Continuous variables were presented as mean ± SD or median (range), and categorical variables were presented as absolute numbers and percentage. Data was checked for normality before statistical analysis using Shaipro Wilk test. Normally distributed continuous variables were compared using Student's t test or ANOVA with appropriate post hoc tests. Categorical variables were analyzed using the chi square test. For all statistical tests, a p value less than 0.05 was considered to be significant.

OBSERVATION

The data pertaining to eighty six (86) patients who were monoinfected with HCV and failed to achieve sustained virological response was analyzed. Out of the total 86 patients, there was clear cut male predominance i.e. 54 (62.79 %) with rural background (villages) i.e.73 (84.88%). The age distribution in these 86 patients varied between 10-80 yrs of age and characterstically peak was seen in 31-40 yrs age group i.e. 25 patients (29.06 %). The major chunk of patients was in 20-50 yrs age group i.e. 67 patients (77.90 %) and none patient was below 10 yrs of age. On analyzing HCV viral load, there was a wide variation from 10^{2} - 10^{9} I.U./ml with mean of 10^{5} I.U./ml. The majority of patients had high baseline HCV viral load (> 4 lakhs I.U. /ml) i.e. 52 patients (60.46%). Out of total 86 patients, 50 patients (58.13%) were cirrhotic, 34 patients (39.53 %) were smokers, 33 patients (38.37%) were alcoholic, 26 patients (30.23 %) had past history of surgical intervention, 9 patients (10.46 %) were diabetic, 9 patients (10.46 %) had got tattoo, 8 patients (9.30%) had history of previous blood transfusion and 13 patients (15.11%) gave history of use of alternative medications.

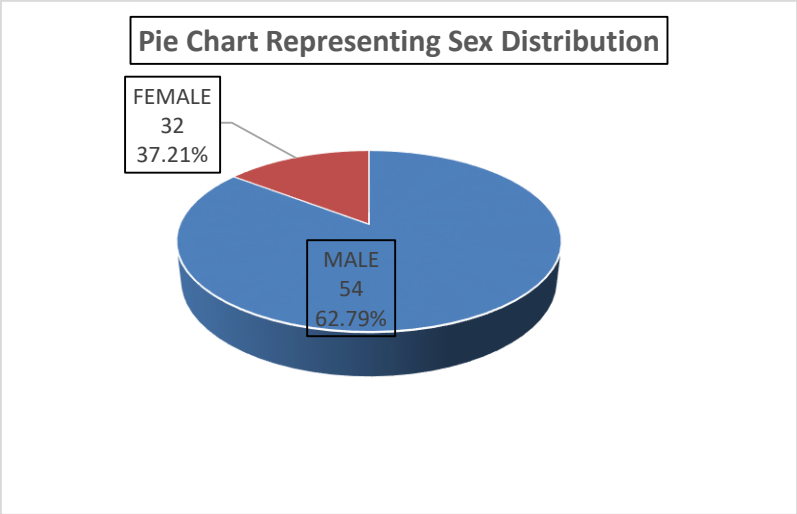

Figure 1- Showing Sex Distribution In SVR Failed Patients

Table-1- Showing Age Distribution in SVR Failed Patients

Age Group	10-20 yrs	21-30 yrs	31-40 yrs	41-50 yrs	51-60 yrs	61-70 yrs	71-80 yrs
Total Patients	2 (2.32%)	18 (20.93%)	25 (29.06%)	24 (27.90%)	11 (12.79%)	5 (5.81%)	1 (1.10%)

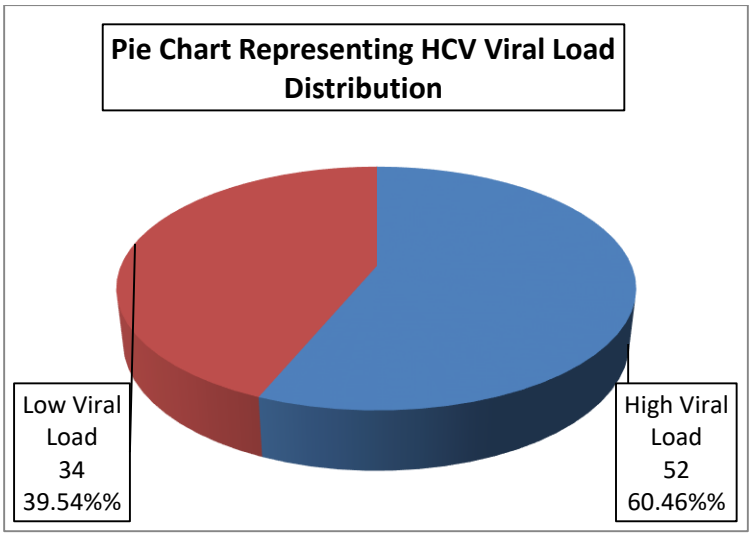

Figure 2- Showing HCV Viral Load Distribution

Table-2- Showing Risk Factors In SVR Failed HCV Patients

Risk Factors	Age 20-50 yrs	Alcohol	Smoker	Diabetes Mellitus	High Viral Load	Rural Background	Cirrhotic
Total Patients	67 (77.90%)	33 (38.37%)	34 (39.53%)	9 (10.46%)	52 (60.46%)	73 (84.88%)	50 (58.13%)

DISCUSSION

High baseline serum HCV-RNA predicted SVR in chronic hepatitis C patients treated with peg interferon–ribavirin **(21,22)** and later on with some DAA, such as boceprevir or sofosbuvir **(23,24).** Whereas thresholds around 800,000 IU/mL seemed to best discriminate good and poor responders using interferon-based regimens **(21-23),** a greater threshold at 6 million IU/mL was proposed to best discriminate treatment outcomes in patients treated with sofosbuvir–ledipasvir **(25,26)**. Accordingly, the FDA recommended extending the length of therapy from 8 to 12 weeks in chronic hepatitis C patients with high viremia treated with sofosbuvir–ledispasvir **(25**). Similar

results have been obtained using other all-oral DAA combinations, such as sofosbuvir–simeprevir, sofosbuvir–daclatasvir, or grazoprevir–elbasvir, although thresholds at 4, 2, and 0.8 HCV-RNA million IU/mL, respectively, have been proposed as best discriminatory values for outcomes generally using shorter treatment lengths **(27-29)**. In our study group also, high HCV RNA viral load i.e. more than 4 lakh I.U./ ml was seen in majority of patients (56 patients, 60.86%). There was wide variation of HCV viral load from 10^{2} - 10^{7} I.U./ml with mean of 10^{5} I.U./ml. Hence, our study highlights that high HCV RNA viral load can be cause of SVR failure in HCV patients. In the era of treatment with Pegylated Interferon and Ribavarin, Genotype 1 & 4 were thought to be difficult to treat, hence were treated with 48 weeks treatment in comparison to Genotype 3 which was treated for 24 weeks. Later on the situation totally reversed and now Genotype 3 is thought to be difficult to treat with more chances of treatment failure in comparison to other genotypes. In our study group, as per National Viral Hepatitis Control Program (NVHCP), genotype testing was stopped, in view of treatment with pan genotypic drugs. Hence only in the first half of patients, genotype testing was done and in them genotype 3 was predominant. In view of lack of genotype testing in all of the patients, we cannot conclusively say about increased risk of developing SVR failure in genotype 3 but it hints at the same and our this finding is in alignment with previous study **(30)**. Several host factors have been clearly linked to fibrosis progression in patients with chronic HCV infection which can affect achievement of SVR and include age above 40 years at time of infection, ongoing alcohol consumption, elevated serum alanine aminotransferase (ALT) level, severe inflammation on liver biopsy, hepatic steatosis etc. Several studies suggested exposure to HCV at a young age is associated with a reduced rate of fibrosis progression **(31-35).** In our study group, there was predominance of SVR failed patients in younger age group i.e. 20-50yrs which can also be due to the reason that maximum number of patients in total pool of treated group belonged to this age group only. Hence, we cannot conclude that younger age is associated with non achievement of SVR. Many studies in which liver biopsies were obtained from patients at least 2 to 3 years apart, showed that severity of inflammation was associated with more rapid fibrosis progression **(36).** As severe liver inflammation is associated with an elevation in serum ALT levels, thus persons with elevated serum ALT levels have a greater prevalence of cirrhosis than those with persistently normal serum ALT levels **(37-39**). The severity of hepatic dysfunction and portal hypertension appears to influence the response rate to DAA, with SVR been greater in Child B than C **(40-44)**. The reason for the lower response in decompensated cirrhosis may be related to shunting, altered drug metabolism, and/or the presence of viral sanctuaries within the markedly cirrhotic liver. Preliminary data suggest that SVR rates in this subset of patients may be enhanced with longer treatment duration (roughly 24 weeks) and/or adding ribavirin **(45,46)**. In our study group also there was predominance of cirrhotic patients i.e.50 patients (58.13%), in treatment failure patients. Alcohol consumption is one of the most important factors driving fibrosis progression in patients with chronic HCV infection. Patients who consume alcohol on an ongoing basis appear have a greater prevalence of cirrhosis and indirectly on SVR achievement than those who consume alcohol either not at all or only rarely **(47-49).** In our HCV study pool also, intake of alcohol was found to be risk factor associated with SVR failure and was seen in 33 patients (38.37%). Most studies have observed an interaction between cigarette smoking and HCV infection on the risk of development of hepatocellular carcinoma (HCC) which develops after developing cirrhosis**(50-53)**. The effect of cigarette smoking on persons with anti-HCV may involve promoting the progression from hepatitis to cirrhosis or from cirrhosis to HCC. It is well proven fact that smoking leads to increased replication of HCV virus and can influence SVR. In our study group also, as 34 patients (39.53%) were smoker. Recently, an association between diabetes mellitus and HCC (or HCV) has been reported **(54,55)** which can be explained on basis of effects of diabetes mellitus on liver, as an arm of metabolic syndrome. In 75% of diabetic patients, fatty liver is seen which can progress to Non alcoholic steatohepatitis and cirrhosis. Thus presence of HCV infection in background of diabetes mellitus becomes more lethal for liver and chances of development of cirrhosis and failed SVR are increased. In our study group also, out of total 86 patients, 9 patients (10.46%) were diabetic. In our study group, there was predominance of males (54 patients, 62.79%) and rural background (73 patients, 84.88%). The males predominance in our group is equivalent to their representation in total pool of treated group but rural predominance is definitely more on comparison with total group of treated patients. It has already been proved that males, that too of rural background are exposed to more risk factors for developing HCV. There are limited health care facilities at village level, hence majority of population is treated by unqualified practitioners who do not follow safe needle practices. Moreover, as they belong to poor socio-economic status and have lack of awareness, thus timely detection of HCV infection is not done and in many patients, they are diagnosed to be suffering with HCV in cirrhotic stage. Thus, our study points in direction that males, especially belonging to rural background can be a risk factor for developing cirrhosis in HCV patients. There are certain well proven risk factors for getting infected with HCV which were also seen in our study like 26 patients (30.23 %) had past history of surgical intervention, 9 patients (10.46 %) had got tattoo, 8 patients (9.30%) had history of previous blood transfusion.

RESULTS

The direct risk factors associated with development of failed SVR in HCV patients are high baseline HCV RNA viral load, cirrhosis, rural background and indirect risk factors are smoking, alcohol and Diabetes Mellitus but large scale studies in future are required to confirm the same.

Statement of Ethics - The authors have no ethical conflicts to disclose.

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