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Efficacy of Sovaldi and Rabavirin Combine Therapy in Chronic Hepatitis C Patients in District Peshawar, Khyber Pakhtunkhwa

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ABSTRACT

The efficacy of Sovaldi and Rabivirin Combine therapy in chronic Hepatitis C patients were determined and also find out factors such as gender and age that can influence response to antiviral therapy. A quasi–experimental Study were carried out in Gastroenterology and Pathology department, Hayatabad Medical Complex (HMC), Peshawar, from February 2016 to July 2016. Patients were given 400 mg oral Sovaldi and 800- 1200 mg oral Rabavirin two doses in a day for a period of 180 days. At the end of treatment the response of the combine therapy was depicted from the negative RNA of HCV by PCR after 24 weeks of treatment. Factors like age, gender and serum ALT were examined of the patients and determined the relations of these factors with the efficacy of Sovaldi combine with Ribavirin. Total 113 patients age up to 60 years, were given combine treatment that full filled the inclusion criteria. Sovaldi and Ribavirin in combination therapy showed better response compare to other drugs. Females and young age patients were favorable responders.

Keywords: *Sovaldi, Rabivirin, Serum ALT, PCR, HCV*

INTRODUCTION

Hepatitis C Virus (HCV) which is the main cause of liver diseases including hepatocellular carcinoma and liver failure [1]. It infects about 180 million people all around the word [2]. Hepatitis C virus is one of the main cause of liver diseases all over the world [3]. HCV belong to family flaviviridae which is an RNA virus with a diameter ranges from 40-50nm. HCV genome is a single stranded RNA molecule of 9500 kilo Daltons [4]. HCV, a big problem for the whole world and about 3.3% of world populations are infected with HCV [5].

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In Pakistan HCV has infected round about 10 million people [6]. In USA it is also the main cause of liver disease and was the main reason of liver transplantation in USA till 1996. Currently from 8000 to 10,000 deaths are occurred in USA each year from HCV. And yearly death ratio is estimated to be raised from 30, 000 per anum to 40,000 per anum by the year 2016 due to chronic liver cirrhosis [7]. The ultimate cause of HCV is liver cirrhosis and hepatocellular carcinoma [8]. Egypt is considered at the top as far as prevalence rate in the world is concern. Egypt has more than 15 % of the infected population [9].While Africa continent according to WHO has the most prevalence of regional HCV which is 5.3% [10].

Despite of the modern and latest laboratory technique and apparatus for screening of blood, blood transfusion remains the main cause of transmission of HCV infection, because the unscreened blood are still used in most part of the world. That's why HCV is a blood borne infections. Unhygienic, poor and unsafe injection practices, use of unsterilized surgical apparatus are the most risk factor and cause of HCV transmission in the world. As hepatitis C virus is the main health problem, causing fatal liver cirrhosis and hepatocellular carcinoma in Pakistan [11].An estimated infected people in Pakistan are 4.9 % and the genotype 2 and 3 are predominant in Pakistan [12].Which required 6 months treatment [13].

The treatment plan for the hepatitis C virus disease is, rapidly evolving to get the most satisfactory response and eradication of virus in long term. For this reason, interferon-alpha 2b was the first drug introduced in the market in 1986 for treatment of HCV. The response rate with monotherapy of interferon was 10 – 20% [14]. Later it was noticed that Ribavirin addition to it, its response increases. Result showed that the result of the combine therapy was 26% more compare to monotherapy [15]. But majority of Pakistani population cannot afford Pegylated interferon, thus standard interferon is used by the patients [16]. Apart of 20 different brands of interferon, other drugs like Ribavirin and Sovaldi are also used in Pakistan.

FDA in 2013 approved Sovaldi in combination with others drug for treatment of genotype 2 and 3 of HCV. For genotype 1 and 4 triple treatment, Sovaldi plus interferon and Rivavirin are used [17]. Sofosbuvir (brand name Sovaldi) is a nucleotide analog used in combination with other drugs.

Sovaldi is marketed in 2013 and has higher rate of cure with less side effects. Sovaldi is an RNA polymerase inhibitor drug, hepatitis C virus use polymerase enzyme to replicates its own RNA during the course of disease. Ribavirin is the nucleoside analog 1-3-D ribofuranogy- 1, 2, and 4 – Triazole -3 – Carboxamide also known as virazole that exhibits antiviral activity against RNA viruses in cell culture [18]. Sovaldi which is 400mg daily once orally drug while Ribavirin is given twice from 800 -1200 mg daily orally depend upon the weight of the patient.

The assessment of the efficacy of the drug for primary treatment, a method devised by Japanese Ministry of Health and welfare, described by Yano [19]. A responder

of HCV RNA is defined when a patient has two consecutive undetectable (<100 copies/ml) values. If for 6 months, when HCV RNA result come as negative, then the patient is assigned as sustained response (SR) that does not need second time treatment. In case when the result of HCV RNA come as positive, then the patient is grouped as incomplete response (IR) or partial response (PR), depending upon ALT (Alanine aminotransferase) is normal or Partially responsive (PR). ALT response is defined as 2 consecutive normal ALT values i.e <48IU/L.

RESEARCH METHODOLOGY

Study design and place:

This quasi-experimental study was conducted in the Hayatabad Medical complex (HMC), prevention program of HCV by Gastroenterology and pathology department MTI/HMC, Peshawar Hayatabad. Adult patients of both the gender and age up to 60 years that are infected from HCV virus were studied in this research. All the enrolled patients had detectable levels of RNA of HCV in their blood serum by polymerase-chain- reaction (PCR).

Exclusion criteria

In this study, all the patients would have been excluded if there would have been chances of decomposed cirrhosis, patients that have HIV and HBV infection, that have transplanted organ before, that have received any prior anti HCV therapy, patients that have psychiatric disease, serious heart disease and uncontrolled diabetes.

Inclusion criteria

The normal blood count, RBC, WBC, platelets were also considered. Sovaldi 400mg once a day and Ribavirin 800mg (<75 kg body weight) or 1200mg (>75 kg body weight) pills in two divided doses a day were given to the HCV patients for a 6 months period. For the detection of HCV RNA, PCR has been done before and after the treatment. All proper follow-up of all the patients was ensured after their clinical test. Biochemical and Hematological assessment were finding out of these patients. At the end of 6 months, over all efficacy of Sovaldi and Ribavirin combine therapy was calculated by non-detectable HCV RNA by PCR and the effects of the patients related factors like gender, age and serum ALT were determined and analyzed by applying Chi-Square test, and using SPSS 19.0 Statistical program. In this statistical program, significance were kept below than 0.05 P-value. If value is more than 0.05 then it will be considered as insignificance.

The efficacy of the drug was measured from the end treatment response (ETR). According to NIH, the end treatment response was defined as, at the end of therapy when the patients had undetectable serum HCV RNA levels. Those patients who had HCV RNA detectable after 24 weeks treatment was considered as non-responders patients.

RESULTS AND DISCUSSIONS

A total of 124 HCV patients from district Peshawar were included having chronic hepatitis C. In those 124 patients, 113 patients had completed their treatment and come back with ETR reports. The remaining 11 patients had stop medication due to financial problem or health related issue.

In those patients 74 (66%) were males and 39 (34%) were females. Their ages ranges from 21 to 60 years. Out of all these 113 patients 98 patients showed respond to the combine therapy of Sovaldi and Rabivirin, which was depicted from the negative values of PCR. In which 86.72% patients showed respond among them female showed 89.74% respond better than male which is 85.13%. So, on the basis of gender, female patients showed high response as compare to the male, which was not significant statistically (P>0.05. i-e = .492).

Table 1: Base line characteristics of responders and non-responders patients.

Characteristics	Responders	Non-responders	p-value
Total 113	98 (86.72%)	15 (13.27%)	-
Age (years)			
≤ 40 51	45 (88.23%)	6 (11.76%)	0.04
>40 62	53 (85.48%)	9 (14.51%)	
Gender			
Male 74	63 (85.13%)	11 (14.84%)	0.492
Female 39	35 (89.74%)	4 (10.25%)	
Gender age (≤40 & >40)	30 (85.71%)	5 (14.28%)	
Male ≤40 35	33 (84.61%)	6 (15.38%)	-
>40 39	15 (93.75%)	1 (6.25 %)	
Female ≤40 16	20 (86.95%)	3 (13.04%)	
>40 23			
ALT (IU/L)			
≤40 20	16 (80%)	4 (20%)	
41-80 50	45 (90.00%)	5 (10.00%)	0.044
81-120 27	25 (92.59%)	2 (7.40%)	
>120 16	12 (75%)	4 (25%)	
Weight (kg)			
≤70 69	59 (85.50%)	10 (14.49%)	0.633
>70 44	39 (88.63%)	5 (11.36%)	

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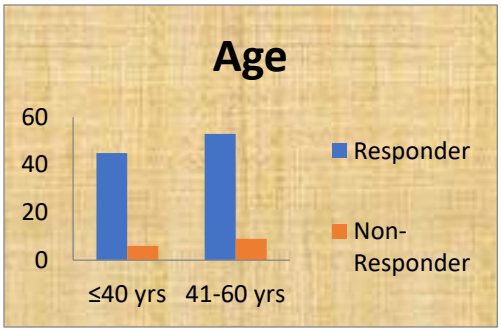

Figure 1 Shows age wise response to drug

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Figure 2 Shows weight wise response to drug

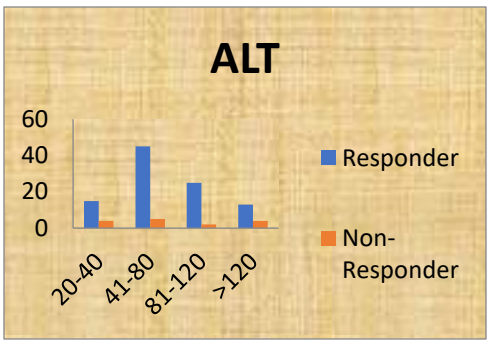

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Figure 3 Shows ALT wise response to drug

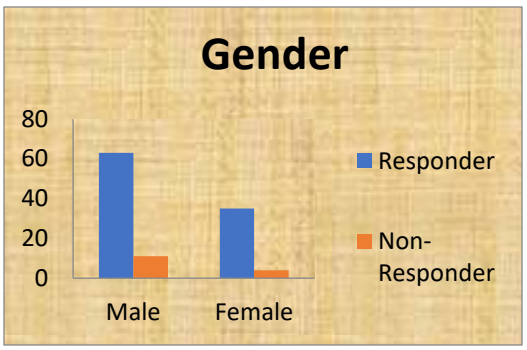

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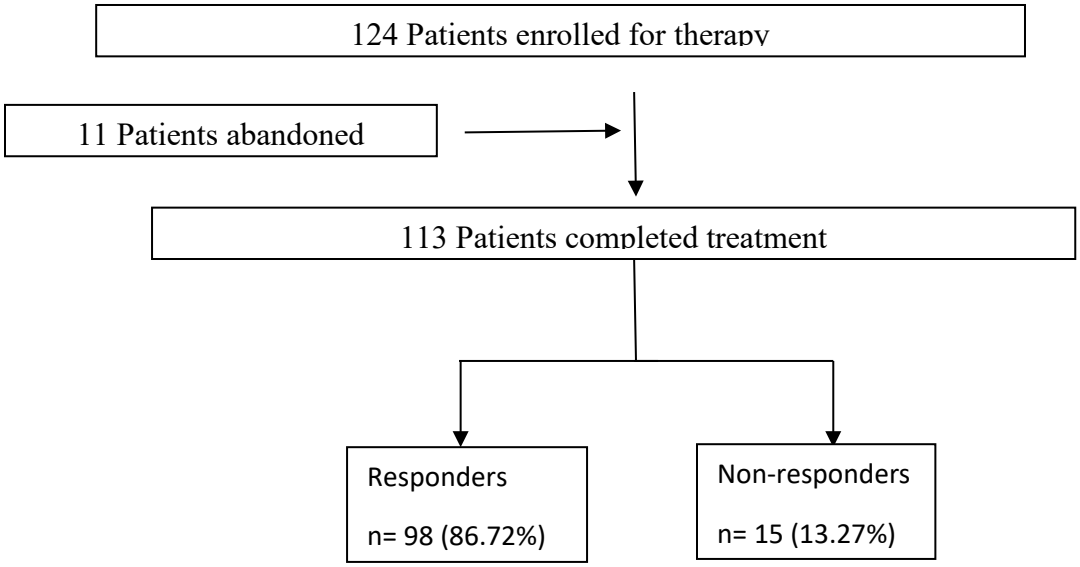
Figure 4 Gender wise response to drug

This Research indicates that younger patients having age less or equal to 40 years, are good responders to the combined therapy of Sovaldi and Ribavirin. Above then 40 years of age, the respond of the patient's decreases considerably, with the age increases as shown in Fig 1.

Patients having weight equal or less than 70kg showed 85.50% respond to the combine Sovaldi and Ribavirin treatment, while the patients having weight greater than 70 kg showed response 88.63% higher than the patients having weight up to 70kg which is statistically not significant (P-Value= 0.633) as shown in Fig 2.

From the ALT levels it is indicated that the patients of HCV showed better respond to Sovaldi combine with Rabivirin drug at markedly high ALT levels. ALT levels increased from the normal i.e. 40 IU/L up to 120 IU/L, than the patients shown good respond i.e. 90% when the ALT range between 41-80 IU/L and 92.59% when it is raised from 80-120 IU/L levels. These show slightly greater ALT levels, good will be the

respond. Further the respond of the patient to the drug decreases, when ALT levels elevated from 120 IU/L i.e. decreased to 75 %. This data is found statistically significant. Thus it is concluded that a slight increase in ALT values induces good result in HCV patients. But at a very high ALT level the respond to the drug is considerably decreases as shown in Fig 3.



To select the best treatment, respond in chronic Hepatitis C patients are utmost important. This will help to treat the patients of HCV properly and to find the responders and treat only those patients. In the same way it is highly desirable to find out the biological non-responders in order to abundant their treatment at the start of the treatment because this will not only reduce the cost of the treatment that will help the patient financially but also the adverse effects of the drugs can be avoided.

Keeping all these things in mind, so many pretreatment factors both related to the patient and also related to the virus are evaluated to find out the successful HCV treatment. These factors are co-related and examined clinically related to Sovaldi combine therapy with Rabivirin.

For the patients with genotype 2 and 3 which is predominant in Pakistan, recently FDA- recommended Sovaldi treatment for 24 weeks thus no longer recommended PEG-IFN/RBV treatment [20]. Because PEG-IFN causes some health complications in the patients thus its use should be reduced or abandoned. Sovaldi the safer drug, should be used for HCV treatment. HCV with genotype 2 and 3 are approximately 30% worldwide [21]. Genotype 3 infected patients show less response, to PEG/IFN [22].

Combination therapy of Sovaldi and Rabivirin increase the response rate for genotype 2 and 3. Response rate in Pakistan for Sovaldi and Rabivirin combine treatment is found in this research which is more than 85%. Genotype 1 and 4 which is mostly present in America and Europe, the response rate found is more than 80% [23].

This study revealed that 98 patients, out of 113 showed response i.e. 86.72% which is depicted from the negative result of PCR. The previous studies indicate that combination therapy in South Asia is the best treatment regime because of genotype 2 and 3 prevalence [24].

Female patients showed better response as compare to the males. Out of 39, 35 showed significant response thus their response rate is nearly 90% as compare to the males which are 85% responders. But this is insignificant statistically. Also the younger patients showed good response as compare to the older one, younger patients age were taken up to 40 years. The good respond shown by younger patients are due to their better immune system and adhesion to the treatment. The older patients showed less response to the therapy and thus have less sustained response regardless of their genotype and other characteristics. Weak immunological response, adverse condition of the disease and other medication use in the old age can reduce the response of the drug. That is why younger patients are good responders to combine therapy of Sovaldi and Rabivirin.

Weight of the patients showed that Patients having weight greater than 70 kg are good responders compare to patients having weight less than 70 kg. But this finding is statistically insignificant having greater P-value than 0.05.

This research also determined that the patients that have slightly or markedly high ALT showed better respond as compare to the normal or elevated ALT levels. Patients having ALT levels between 81-120 IU/L showed greater respond to the drug (92%) as compare to elevated ALT (75%). This difference might be due to the extent of hepatic damage as the level of ALT in the serum reflects the damage of the liver cells. This finding is statistically significant. Research also indicates that viral genotype present in this part of the world is mainly 3a. Out of 113 patients, 64 patients have 3a viral genotype.

So, this study showed that Sovaldi and Ribavirin is more effective to both genotypes 2 and 3 as compare to 1 and 4 in Pakistan. This present data give rise to the need of further research to test the factors like age, gender, weight and serum ALT that effects the response of anti-viral drugs i-e Sovaldi and Ribavirin before and during the treatment on a large scale. I have taken only 113 patients, because Sovaldi is newly marketed in Pakistan, thus the number of patients using this drug are quite limited and many patients still not completed their six months treatment to till date. Secondly the efficacy of this DAA drug can be depicted after 12 weeks of treatment rather after 24 weeks of treatment which may make the research easier and more result oriented.

CONCLUSION

The oral Sovaldi and Rabivirin combine therapy in chronic Hepatitis C patients has sustained virological response. This combination treatment is interferon free which has so many side effects in patients. Further the patient related factor like gender, age, weight and serum ALT levels to a large extent can predict the response of Sovaldi and Rabivirin combine therapy before and during the therapy. But strictly speaking, gender

has no such prominent effect on the response of combination therapy of Sovaldi and Rabivirin. Young age in both genders, high weight in males and high level of ALT favors the response to this antiviral drug.

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