Triple Regimen Therapy Response in HCV Patients of Genotype-III

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ABSTRACT

Background: It is always a topic of interest of the health care providers and patients to get a treatment option that is most safe and less time consuming. Hence, HCV which is a fatal disease has been dealt with by different treatment options and an effort was made ever to explore less time consuming and more effective treatment options. Although this practice has been done in Europe, the efficacy of this was deemed to be checked in Pakistani population.

Objective: The aim of the study was to determine the efficacy of triple regimen therapy for the treatment of HCV patients.

Methodology: This was a descriptive case series study that was conducted at National Hospital in Faisalabad in duration of 1 year. An informed consent was taken before enrolling the patients. A total of 34 cases of HCV who were found positive on the ELISA and PCR were selected from the outdoor department. Patients of any gender and age greater than 18years, treatment naïve, relapsers and non-responders to conventional interferon and/or pegylated interferon were included in this study. All those patients who had HCV along with HCC, elevated bilirubin, elevated renal function tests and who were otherwise suffering from other chronic diseases such as Rheumatoid arthritis were excluded from this study. Effectiveness of the treatment was considered by confirming the absence of HCV by PCR at 12 weeks of treatment (EVR) which is also the end of treatment period in this study. However, RVR was also assessed at 4 weeks of treatment. Data was analyzed by using SPSS 20.inc.

Results: Mean age of the patients was 44.54±10.32 years. RVR was achieved in 94.12% (32 patients). 5.88% that is 2 patients could not achieve RVR (one was lost to follow up and the other one remained positive for PCR after 4 weeks). While 97.6% (33 patients) achieved EVR and 2.94% (1 patient) was lost to follow up.

Conclusion: It is concluded that triple regimen therapy is equally effective, as it has been mentioned in international studies and is recommended that the treatment shall be persuaded in Pakistani population as it is being practiced in other countries of the world.

Keywords: ELISA, HCV, PCR, Pegylated Interferon, Ribavirin, Sofosbuvir, Triple regimen therapy

1 INTRODUCTION

Viral Hepatitis C has no boundaries and found to be present in almost all parts of the world. On the other hand, the health care providers and researchers are trying to explore the most powerful weapon against this disease in terms of medicine. Hepatitis C virus infection is associated with increased morbidity and mortality in patients.[1]

Chronic hepatitis C develops in 85% of patients who get exposed to hepatitis C virus. Most patients acquire this sub-clinically from parenteral route. This is clinically indistinguishable from chronic hepatitis due to other causes. This is the most common form of chronic hepatitis. More than 170million people are infected worldwide (CMTD 2016,[2]. In Pakistan, The prevalence of HCV in general population is 4.9%.[3] Regarding distribution of HCV genotype 79% are genotype 3 and most of the rest are genotype 1. Genotypes 2, 4, 5 and 6 are less common.[4]

Standard therapy for HCV infection from the late 1990 to the early 2010 was a combination of Peg interferon + ribavirin. The introduction of direct acting and host targeting antiviral agents is rapidly expanding the therapeutic armamentarium against HCV. The treatment of chronic hepatitis C has undergone revolutionary change with the availability of 1st generation earlier and recently the 2nd generation direct acting antiviral agents (DAAS). American and European authorities (FDA and EMA) have approved second generation DAAS to be used in clinical practice. Sofosbuvir approved against genotype 1, 2, 3 and 4. It is effective in treatment naive, treatment experienced, compensated cirrhosis patients and patients with HCC awaiting liver transplant patient in a healthcare setup.[5]

Diagnosis of HCV infection is usually a two-step process, identification of HCV antibodies followed by demonstration of viremia. The most common serological test for detecting HCV antibodies is by an Enzyme linked immunosorbent Assay (ELISA) which has a sensitivity and specificity of 95%. A positive ELISA almost always represents either active viral infection or resolved HCV. Confirmation of active infection in any patient with a positive anti-HCV (ELISA) requires the detection of HCV RNA by PCR. [6]

New direct acting antivirals DAAs have brought a revolution in hepatitis C treatment offering oral regimens that are simple, better tolerated and much more effective than the old interferon based therapies. Unlike interferon, the DAAs work both for HIV positive and for HIV negative people, although people with HIV/HCV co-infection need to exercise caution about potential drug-drug interactions with anti-retroviral.[7]

According to Sulkowski, hepatitis C therapy could soon go from 18 pills a day and a weekly injection to only one or two pills daily. By demonstrating high rates of use in the absence of interferon alfa [peginterferon] injections and ribavirin pills, this study paves the way for easier, more effective treatments for chronic hepatitis C infection. [8]

So far, the standard therapy of a chronic HCV infection consisted of Pegylated or regular interferon Alfa as a single therapy or in combination with ribavirin. After approval of two protease inhibitors, boceprevir and telaprevir, in 2011, the standard therapy for patients with genotype 1 changed. Triple therapy protocols were developed by maintaining the standard therapy consisting of interferon Alfa and ribavirin, by adding one of the new protease inhibitors.

With the triple therapies, a relevant increase in sustained virologic response (SVR) rates was observed. The SVR rates in therapy naïve patients increased from 40% to 67% [9] and, in formerly treated patients, from 21% to 59-66%.[10]
Due to unsubstantial of literature supporting the effectiveness of triple regimen therapy in Asian population, this study was planned and executed. This can affect the opinion of the health care providers for management of patients with HCV.

2 METHODOLOGY

This is prospective case series study that was conducted in National hospital Faisalabad in duration of one year started from April 2015 to May 2016. A total of 34 cases were enrolled in this study after carefully following inclusion criteria. This sample size is generated using 95% confidence interval, 5% margin of error taking an expected percentage of HCV as 5%. Inclusion criteria was I) patients of age >18 of both gender having anti-HCV positive on ELISA and HCV detected on PCR qualitatively without discrimination of genotype, ii) Treatment naïve, replacers after conventional interferon therapy or Peg-interferon therapy, iii) non responder to either of these therapies or both were included in this study. Patients who have abnormal renal function test, raised serum bilrubin >3mg/dl, prolonged prothrombin time >3sec, hb below than 12g/dl or raised TSH, decompensated cirrhosis (decompensation was defined as bilirubin >3, serum albumin <2.5g/dl, presence of ascites) were excluded. We also excluded the cases having hepatocellular carcinoma at the time of presentation or any other chronic condition.
Patient informed consent was taken related to the expenses on follow-up visit, medical tests and medication. Strong follow-up was made possible by obtaining postal address along with contact number of the patient.
Baseline investigations were carried out the time of presentation like age, gender, biochemical profile, ELISA and PCR for HCV. Ultrasound was also carried for confirmation of ascites to exclude patient. Patients were advised to take sofosbuvir 400mg once daily, ribavirin depending on their body weight (above 75kg 1200mg/day, <75 1000mg/day) with weekly subcutaneous injection of PEG-interferon. Paracetamol was advised in case of fever and pains.
The patient were instructed to come for follow-up visit after two weeks with their blood profile and to bring the remaining doses of prescribed medicine to check the proper compliance. After two week questions were asked related to any complaints during treatment duration and recorded. After four week of treatment CBC and their Qualitative PCR were carried out to check the rapid virological response. At week 8th CBC and platelet count were checked. At week 12th cases evaluated for HCV by PCR qualitative along with CBC and platelet count. This was recorded as EVR (early virological response). This EVR was also considered as ETR. All this information is collected on a proforma. SPSS 20 was used for statistical analysis to generate results.
Patients were evaluated after 4 week and 12 week of treatment. Data was analyzed by using SPSS 20.inc.

3 RESULTS

There were total 34 cases with positive hepatitis C on Elisa and PCR. The mean age of the patients was 44.54±10.32 years. Baseline parameters are mentioned in the table# 1. It was found that out of 34 cases with HCV 32 patients (94.12%) achieved RVR (rapid virologic response), while 2 patients (5.88%) did not Achieve RVR. After 3 months of treatment there were 33 Patients (97.06%) who were achieved EVR which is also the ETR for this study. While just 1(2.94%) patient was lost in the follow up. Data was stratified for the type of patients so that actual reflection of the treatment could be observed and mentioned in Table#2.

4 DISCUSSION

Sofosbuvir, a newly developed drug that received approval from the FDA in December 2013. The pill, which was developed by Gilead Sciences, has been billed as one of the first examples of a new generation of drugs that stand to make hepatitis C history. By "distinguishing" itself as a piece of RNA, the drug shuts down the virus' replication process, allowing the body to clear the infection once and for all.[11]
According to Centers for Disease Control and Prevention, hepatitis C currently affects 3.2 million people in the U.S. alone, making it the most common blood-borne infection in the nation. [12]
In order to put a barrier for recurrence of HCV in treated patients which were increasing in number a novel treatment was introduced. This novel treatment has resulted in addition of sofosbuvir along with interferon and ribavirin among the infected patients. [13]
Clearly, additional effective therapies are warranted. Insights into HCV virology have identified viral targets for potential novel therapeutics. This new approach to HCV therapy uses a direct antiviral mechanism. The HCV NS3 protein, in addition to its cofactor NS4A, form a serine protease that cleaves the posttranslational HCV polyprotein into 4 nonstructural proteins. One of these proteins is NS5B, which encodes the HCV RNA polymerase. Furthest along in DAA development, there are two NS3/4A protease inhibitors that have recently completed phase 3 trials and were approved in combination with pegylated interferon with ribavirin. SVR rates for genotype 1–infected treatment-naive noninfected patients are as high as 66%–75% with triple combination therapy. [10,14]
Combination therapy with PEG-IFN and RBV produces an SVR in no more than 50% of genotype 1 HCV-infected patients, compared to 70–80% of patients infected with genotypes 2 and 3. This and other limitations of dual anti-HCV therapy, such as the long treatment duration (48–72 weeks) and the many side effects of both PEG-IFN and RBV, have resulted in the development of some new promising molecules named DAAs.[15]

The treatment of patients with HCV genotype 3 has remained a clinical challenge in the era of direct-acting antiviral agents. Patients with HCV genotype 3, especially those who have not had a response to previous treatment and those with cirrhosis. [16]

In a study conducted by Zeuem S et al it was stated that the efficacy of the tripe regimen which include sofosbuvir along with ribavirin and peg-inerferon the majority of the patients were female and efficacy was noted in 99% of cases at 4th week of treatment. The study population of this study matches to the above mentioned study as majority of the cases were female in this study. Among patients with HCV genotype 3 who received 24 weeks of sofosbuvir–ribavirin, 213 of 250 patients (85%; 95% CI, 80 to 89) had a sustained virologic response 12 weeks after the cessation of treatment[17] which was different as noted in our study.

Among patients with HCV genotype 3, the rate of sustained virologic response at 12 weeks after treatment was 95% (95% CI, 92 to 98) among those who had received sofosbuvir–velpatasvir for 12 weeks, as compared with 80% (95% CI, 75 to 85) among those who had received 24 weeks of sofosbuvir–ribavirin. The sustained virologic response rate with 12 weeks of sofosbuvir–velpatasvir was significantly superior to that with 24 weeks of sofosbuvir–ribavirin and this study showed the same results. [16]

In a BOSSON trail it was noted that the triple has effect in terms of treatment of HCV in 97.4% after 4 week of medical treatment and 100% after 12 week of treatment, The results of our study are in accordance with this trial and it further strengthen the opinion to advise triple regimen therapy for the management of HCV in future.[18]

In this study the minor side effects were also reported that were managed as per medical standard and protocols. In a nut shell it is clear that triple regimen therapy is effective not only in remission of HCV but also reducing the treatment duration. So, it could be advised to the patients even if the case is having genotype 3 like in Asian population especially the people in sub continent.

5 Conclusion

Conclusively, it is not wrong to state that triple regime results in more benefit than the double regimen therapy. There are lesser number of cases who are presented with the side effects and relapse.

But studies are still needed on a larger scales to cover the most of the population who has this fatal disease for a deep insight into the efficacy and safety of the triple regime therapy.

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TABLE 1

STUDY CHARACTERISTICS OF PATIENTS

Variables		n (n%)
Gender	Male	9(26.5%)
	Female	25(73.5%)
Platelet count	Normal	33(97.1%)
	Decreased (<150,000)	1(2.9%)
SGPT	Normal	27(79.4%)
	Increased	7(20.6%)
Albumin	Normal	33(97.1%)
	Mild decreased (<3.5 but >3)	1(2.9%)
Genotype	1	3(8.8%)
	3	31(91.2%)
Abdominal Ultrasound	Normal	28(82.4%)
	Abnormal (mild splenomegaly)	6(17.6%)

TABLE 2

RESOLUTION OF HCV IN DIFFERENT TYPES OF PATIENTS AFTER 1 & 3 MONTHS TREATMENT

	Type of patients			
	Naive patients	Relapse after conventional interferon	Relapse after pegylated interferon	No response
Rapid virological response achieved after one month (n=32)	19	7	1	5
	59.4%	21.9%	3.1%	15.6%
End Treatment response achieved after three months (n=33)	21	7	1	4
	63.6%	21.2%	3.0%	12.2%

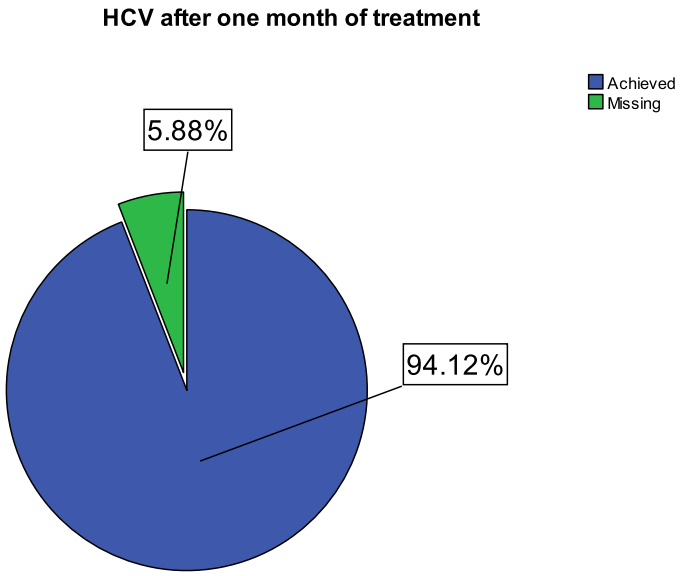

Fig. 1. Efficacy of treatment for resolution of HCV

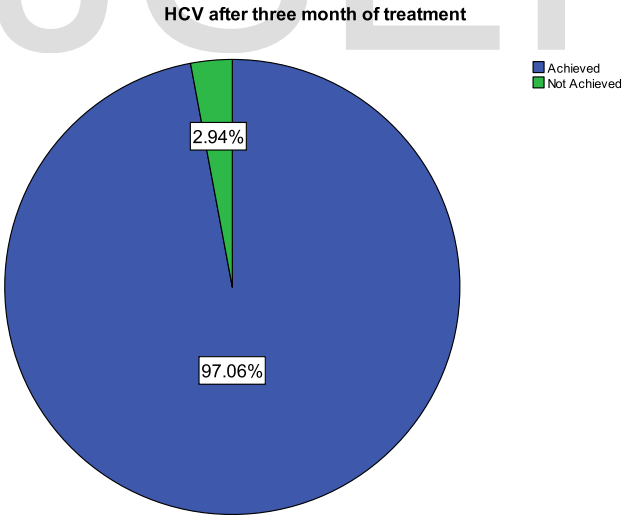

Fig. 2. Effectiveness of treatment of HCV after 3 months