

SOFOSBUVIR RIBAVIRIN COMBINATION THERAPY RESPONSE IN CHRONIC HCV PATIENTS IN KHYBER PAKHTUNKHWA

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ABSTRACT

Objectives: To see the Sofosbuvir Ribavirin combination therapy response in chronic HCV patients.

Material and Methods: This study was conducted in private setup of Hepatitis clinics in collaboration with a private clinical laboratory of Peshawar, Pakistan. The patients were enrolled from July 2016 to December 2017. A total of 65 patients (54 naïve and 11 non-responder/relapser) were enrolled in this study. Age range was 18-70 years while mean age was 36 ± 2 years. For all of the subjects' biochemical profile and PCR tests were done at the start and end of therapy. All patients were given Direct acting antiviral drugs (DAA) drug for six months and after six month of therapy end of treatment response (ETR) was noted.

Results: All the enrolled patients achieved 100% ETR. Alanine amino transferase (ALT) level improved in most of the patients (81%) while there was reduction in Hemoglobin level in 46.5% of the patients.

Conclusions: Response rate in the current study is much higher as compared to previous studies conducted on Interferon based ribavirin therapy.

Keywords: Hepatitis C virus, Direct acting anti viral drugs. Polymerase Chain Reaction. Khyber Pakhtunkhwa

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INTRODUCTION

Hepatitis C caused by hepatitis C Virus (HCV), has affected 170 million people with a prevalence of 3% worldwide. HCV infection may sometime clear spontaneously in 15-30% of the cases but if it persists then it can lead to some serious complications like cirrhosis, hepatocellular carcinoma (HCC) and end stage liver related mortality.¹⁻⁴ In Pakistan, sero-prevalence is different in different parts, ranging from 2.2 to 13.5%. As Pakistan is a developing country, people having low literacy rate and least information regarding diagnostic and treatment procedures, hence HCV has become an economic burden in Pakistan and especially in KPK.⁵

The purpose of treatment of HCV infection is to eradicate virus from the body. In this regard the first treatment option interferon (IFN) based therapy was introduced in 1987, before the identification of HCV as major etiological agent of hepatitis.^{6,7} In order to improve the sustained response, a combination therapy of Pegylated interferon (Peg-IFN) plus Ribavirin (RBV) was introduced and for many years this was followed and was considered as the standard of care for the treatment of chronic HCV infection.^{8,9} Different studies showed virological response rate ranges from 36 to 64% according to viral genotypes.¹⁰

The above-mentioned therapy options were associated with more severe adverse side effects and lower response rate. With the improvement of antiviral drugs and introduction of direct acting antiviral drugs (DAA), the treatment of HCV has been changed and subsequently the prognosis of patients. According to viral molecular target, DAA include inhibitors of non-structural proteins NS3/NS4 (simeprevir, paritaprevir and grazoprevir), NS5A ledipasvir (LDV), declatasvir (DCV), ombitasvir, elbasvir, and velpatavir) and NS5B sofosbuvir [SOF] and dasabuvir) these are already available in

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market and even in Pakistani market with reasonable prices. These drugs are promising for the eradication of infection in more than 90% of chronic HCV patients, with limited variations related to viral genotypes.¹¹ Hence the next generation DAA (SOF) was introduced and approved by national health authorities, expecting to be a milestone for the treatment of HCV infection. SOF is an oral nucleotide analogue inhibitor of HCV specific NS5B polymerase, a crucial enzyme in viral replication, with high antiviral activity and safety. Efficacy based on SOF based treatment has been demonstrated in different phases of clinical trials.¹²⁻¹⁵

In Pakistan the trends were to use peg IFN and RBV combination therapy. In Pakistan and even in Khyber Pakhtunkhwa (KPK), many studies have been done regarding IFN based therapy.^{5,16,17} But now with introduction of DAA for the last few years, the physicians' diverted the treatment options toward DAA, although at the start expensive but nowadays with affordable price range. As these drugs have just been introduced in Pakistan and especially in KPK during last few years, limited studies exist to reflect efficacy and response in affected population. Moreover as this therapy is successful in almost all of genotypes, therefore we aimed to highlight the response of SOF based therapy, irrespective of genotype determination in chronic HCV patients in KPK.

MATERIAL AND METHODS

This study was conducted in private setup of Hepatitis clinics in collaboration with a private clinical laboratory of Peshawar, Pakistan. The patients were enrolled from July 2016 to December 2017. This was a prospective study and subjects age was in between 18-70 years. Only those patients were selected who had confirmed viremia (naïve patients) or treatment experienced patients that are relapser or non-responder with the previous IFN based therapy. The included patients were treated with combination therapy of SOF and RBV for six months according to treatment recommendation: The dose of SOF was 400 mg once daily and RBV was based on body weight (1000mg/day for < 75kg and 1200mg > 75kg in a divided dose). The HCV RNA level and other biochemical tests were performed at regular basis at weeks 4, 12 and 24 weeks of treatment. The lower limit of detection of the PCR assay was 10 IU (Abbot Real Time). Liver texture and margins were confirmed by Ultrasonographer having more than 5 years expertise in this perspective. Patient with decompensated liver disease were excluded from the study. Moreover the study was approved by the concerned ethical committee and was conducted according to the protocols/guidelines for good clinical practice and declaration of Helsinki.

RESULTS

All the enrolled patients (65) were treated with SOF and RBV combination therapy for the six months period. A great significant relationship was observed in between DAA and response. All of the enrolled patients including non responders/relapser to the previous treatment (11) and naïve patients (54) achieved 100% ETR. HCV RNA was invariably below the lower limit of detection. There was rapid and great reduction in the ALT level and this was confirmed throughout the length of treatment. Hemoglobin (HB) level was normal in 55 subjects (84.6%) before therapy and was sub optimum in 30 (46.6%) subjects at the end of therapy and the male to female ratio was 0.39: 0.61. All the demographics, biochemical and virological characteristics of enrolled patients are given in table 1.

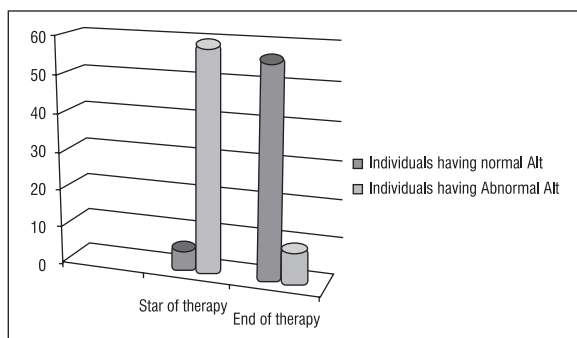
Table 1: Baseline clinical, virologic and laboratory parameters of 65 patients with chronic hepatitis C virus infection

Parameters	Data
Age, years, mean \pm SD (range)	36 \pm 2 (18–70)
Female sex, n (%)	40 (61.5)
Threshold cycle value (ct)	24 \pm 3 (18–33)
Hb Level	
At the start of therapy	55 individuals having normal level/10 individual shaving lower level
At the end of therapy	30 individuals having sub optimum level/35 individuals having normal level
PCR at the start of therapy	65 subjects positive
PCR at the end of therapy	65 subjects negative (100%)
Liver involvement	
ALT, IU/L (n.v. 10–40)	6 individuals having normal level/59 individuals having high level
At the start of therapy	56 individuals having normal level/9 individuals having high level
At the end of therapy	

Table 2: Treatment response in treatment experienced and treatment naïve patients

	Relapser/non responder to IFN+RBV	Treatment naïve patients
Number of individuals	11	54
% Response	100%	100%

Abbreviation: IFN Interferon, RBV Ribavirin



DISCUSSION

After the identification of HCV as the etiologic agent of hepatitis, many efforts have been done for the eradication of HCV. Several studies have evaluated response of IFN based therapy with or without RBV. These studies have consistently reported lower SVR rates in HCV patients. Moreover, IFN based therapy was mostly associated with adverse side effects leading to discontinuation of therapy.⁸⁻¹⁰

The introduction of DAA into the clinical practice for therapy of HCV brought a new horizon to achieve a higher SVR > 90% virtually for all of the HCV infected patients. This outcome can be accomplished with the perspective of viral eradication and no/least side extra hepatic manifestations associated with previous antiviral regimes.¹¹

In the current study, we focused on a single centre experience with the use of DAA for the treatment of HCV. The first striking feature of the study was the highest rate of ETR. All 65 patients get recovered from high viremic stage to non active infection. All of the enrolled patients including non responders/relapser, showed 100% response at the end of six months of therapy. This was in accordance to a study conducted by Gragnani L et, al who reported 100% response rate by using different types of SOF- based antiviral combination confirming high antiviral efficacy using these drugs.¹⁸ According to other studies based on IFN done in KPK, the response rate was too low that ranged from 70-82%.^{5,16,17} The highest ETR noted in the current study might be due to favorable host and viral factors. As the current study involved more numbers of female population as compared to male and the previous studies have already exposed female gender as better host related predictor of response.⁵

ALT level as the biochemical parameter was more significantly influenced by this therapy. As the ALT is a biochemical marker of virus-induced hepatocytolysis, its normalization is obvious associated with reduction or disappearance of viral particles. Similarly as the viral particles are constitutive part of the cryo-precipitating

immune complexes, the formation of such complexes are clearly affected with the reduction of viral particle or viral particles no more exist following administration of DAA.

Looking on to the Hb level, HB level was more in most of the patients (84.6%) prior to therapy but during/ at the end of therapy there was depression in HB level (46.5%). Such correlation has been shown by other studies too in which there was a great regression in HB level. This might be possible side effects of DAA or any of the antiviral drugs.

There was a remarkable improvement in the clinical manifestations, although symptoms persisted despite their achievements of response. In spite of all, the response rate was significantly higher than those obtained with IFN+RBV combination therapy or with triple regimes that included first generation protease inhibitor, with additional advantage of least side effects associated with DAAs.¹⁹⁻²²

Although there was maximum response of SOF and RBV combination therapy, but as this study had just focused on ETR and low number of subjects were included in this study, hence the need exists to explore the sustained virological response (SVR) in case of DAA. Single centre, limited number of patients and non-involvement of patients from government hospitals are other limitations of this study.

CONCLUSION

Our single centre study showed remarkable End of treatment response (ETR) in virtually all patients of HCV, These results are strikingly better than those with previous antiviral regimes for HCV treatment.

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CONFLICT OF INTEREST: Authors declare no conflict of interest

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

- Afridi J:** Provided data for research article.
Mahmood N: Performed experimental Work.
Ali S: designed the methodology
Ahmad B: matured the manuscript and critically reviewed the atricle.
Jalil F: Helped in manuscript Preparation.
Raham Sher: matured the manuscript and critically reviewed the atricle

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.