Original Article

Hematological Side Effects of Sofosbuvir and Ribavirin Combination Therapy in Chronic Hepatitis C patients

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ABSTRACT

Objective: This study aimed to observe the hematological side effects of sofosbuvir and ribavirin therapy in treatment of chronic hepatitis C (CHC) patients.

Study Design: Descriptive study

Place and Duration of Study: This study was conducted at the Outpatient Department of Gastroenterology, Nishtar Hospital Multan from October 2016 to March 2017.

Materials and Methods: It included 117 treatment naive patients with CHC who were given combination therapy of Sofosbuvir and ribavirin. Patients complete blood picture was sent at the baseline and then repeated at 1 month and at 3 months. Drop in mean of all blood parameters was calculated. Cut-off for Significant Side effects were set as follows: Anemia (Hb<10gm/dL), Leukopenia (<4000 WBCs/mm^3), Thrombocytopenia (<100,000 platelets/mm^3). Data was analyzed using the SPSS version 17.

Results: Out of 117 patients, 64 (54.7%) were females and 53 (45.3%) were males. Mean age of patients was 39.28 ± 11.23 years. Mean hemoglobin (Hb), total leukocyte count (TLC) and platelets (PLT) before treatment were 12.51 g/dL, 8.53 x10^3 /mcL and 273 x10^3 /mcL, respectively. Mean Hb and TLC kept on decreasing as the treatment progressed. The decrease in mean of WBC was statistically significant (p<0.001). Mean platelet count increased at 1 month and decreased at 3 months. Significant side effects were observed as follows: anemia was seen in only 3.4% patients, leukopenia in 2.6% patients and thrombocytopenia in 0.8% patients.

Conclusion: Hematological abnormalities are uncommon in sofosbuvir and ribavirin therapy

Key Words: Hematological side effects, sofosbuvir, ribavirin, chronic hepatitis C, pegylated interferon

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INTRODUCTION

Due to high sustained virological response (SVR) rates, sofosbuvir-based regimens are currently a mainstay for hepatitis C virus (HCV) therapies. Chronic hepatitis C virus (HCV) infection affects 3% of the world's population and 1.3% of the United States' population.[1,2] Approximately 130–150 million people globally have chronic hepatitis C infection (CHC).[3] Prevalence in Pakistan is approximately 4.8% and it is among the highest in the world[3] with approximately 10 million people infected with HCV.[4,5] It is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC), and is one of the most common causes of liver transplants in the United States.[2]

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Treatment of CHC has undergone a revolution. Historically, the only therapy available for almost 25 years was interferon in combination with ribavirin, which yielded inconsistent results and serious side effects.[6] The discovery and subsequent development of direct-acting anti-virals (DAAs) heralded a marked improvement in rates of sustained virological response as well as quality of life.[7–12] There has been much research on new anti-virals as add-on therapies to either pegylated interferon (pegIFN) and ribavirin or, more recently, as all oral DAA combination regimes. While interferon-based therapy is now largely being eliminated from the armamentarium of HCV management.[13]

Hematological abnormalities[14] such as anemia, neutropenia and thrombocytopenia are common during combination therapy with pegINF and ribavirin.[5] The side effect profile of sofosbuvir plus ribavirin combination is much better. This study aims to look at the hematological side effects of sofosbuvir plus ribavirin combination in treatment of CHC patients.

MATERIALS AND METHODS

This is a retrospective descriptive study carried out at Nishtar Hospital Multan (NHM). Data was collected

from the Hepatitis Clinic, Outpatient Department of Gastroenterology, NHM from October 2016 to March 2017. The inclusion criteria was all treatment naive patients who had CHC. Patients with Cirrhosis, HCC and those who had both hepatitis B & C were excluded from the study.

Patients were given sofosbuvir plus ribavirin combination. Sofosbuvir was administered orally at a dose of 400 mg once daily along with ribavirin, which was administered orally as a divided dose according to body weight (1000 mg daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight of ≥75 kg).

Patients complete blood picture was sent at the baseline, before the start of treatment and then repeated at 1 month and at 3 months. Mean of the different hematological parameters was calculated. A paired samples t-test was done to compare the differences in mean. A p value <0.05 was considered statistically significant. In our study cut-off values for Significant Side effects were set as follows: Anemia (Hb<10gm/dL), Leukopenia (<4000 WBCs/mm^3), Thrombocytopenia (<100,000 platelets/mm^3). Data was analyzed using the SPSS version 17.

RESULTS

A total of 117 patients, 64 (54.7%) female and 53 (45.3%) male, with chronic HCV infection were included in the study. The mean age of patients was 39.28 ± 11.23 years with range of 17 to 69 years. Table 1 shows the baseline demographic and clinical characteristic of study population. Mean Hb, TLC and PLT before start of treatment was 12.51 ± 1.68 g/dL, 8.53 ± 2.27 x10^3 /mcL and 275 ± 80.0 x10^3 /mcL, respectively.

Table II shows the change in means of Hb, TLC and PLT before staring sofosbuvir and ribavirin combination therapy, and then at 1 month and 3 months of treatment. The mean Hb and TLC decreased as the treatment progressed. Hb decreased from 12.5 g/dL at baseline to 12.4 g/dL at 1 month and then 12.3 g/dL at 3 months after starting treatment. TLC decreased from 8.53 x10^3 /mcL at baseline to 8.33 x10^3 /mcL at 1 month and then 7.31 x10^3 /mcL at 3 months of therapy. The mean of PLT showed a small increase at 1 month and then dropped to 273 x10^3/mcL at 3 months. A paired-samples T-test was done to compare the difference in means. There was a statistically significant difference between mean of TLC before starting treatment and at 1 month and 3 months (p<0.001). The difference in means of Hb and PLT, before and after starting treatment, were not statistically significant (p>0.1).

Our study showed anemia in 4(3.4%) patients, leukopenia in 3 (2.6%) patients and thrombocytopenia in 1 (0.8%) patient (Table 3).

Table No.I: Baseline demographic and clinical characteristic of patients (n=117)

Characteristic	n (%)
Age (years)	
Mean ± SD	39.28 ± 11.23
Range	17 to 69
Gender	
Male	53 (45.3)
Female	64 (54.7)
Mean Baseline Hb (g/dL)	12.51 ± 1.68
Male	13.4
Female	11.8
Previous Treatment Status	
Treatment naive	117 (100)
Relapse	0
Non responder	0
Partial responders	0

Table No.2: Mean of blood counts before and after starting sofosbuvir ribavirin therapy

Variable	*Mean ± SD*
Hemoglobin g/dL	
Baseline	12.51 ± 1.68
At 1month	12.41 ± 1.62
At 3 months	12.3 ± 1.62
P value*	>0.1
Total Leukocyte Count x10^3/mcL	
Baseline	8.53 ± 2.27
At 1month	8.33 ± 2.46
At 3 months	7.31± 2.38
P value*	<0.001
Platelet Count x10^3/mcL	
Baseline	275 ± 80.0
At 1month	276± 83.6
At 3 months	273± 85.1
P value*	>0.1

*Paired samples t-test done to compare the difference in means before and after starting treatment.

Table No.3: Treatment discontinuation and Significant Side Effects reported during the study period.

Variable	n (%)
Discontinuation of treatment due to side effects	0
Significant Side Effects	
Anemia (Hb<10gm/dL)	4(3.4)
Leukopenia (<4000 WBCs/mm^3)	3 (2.6)
Thrombocytopenia (<100,000 platelets/mm^3)	1 (0.8)

DISCUSSION

In this descriptive study the mean Hb and TLC continued to fall through the course of treatment. The mean decrease in TLC before and after treatment was statistically significant (P<0.001). Our study showed that the mean Hb dropped 0.2g/dL (from 12.5g/dL to

12.3g/dL) among patients receiving sofosbuvir and ribavirin. While Foster et al found that the median reduction in Hb level at the end of treatment was 2.0 g/dL and 1.8 g/dL, respectively, among patients receiving sofosbuvir and ribavirin for 16 and 24 weeks.[15]

Pontali et al found anemia (Hb<10g/dL) in 12.9%, neutropenia (<1000 neutrophills/mm^3) in 42.8% and thrombocytopenia (<100,000 platelets/mm^3) in 39.1% of HIV-HCV co-infected patients undergoing pegylated interferon and ribavirin treatment.[16] Our study showed anemia in only 4(3.4%) patients, leukopenia in 3 (2.6%) patients and thrombocytopenia in 1 (0.8%) patient. The severe side effect profile of the above mentioned study was not only due to interferon based therapy but also due to the fact that the sample was co-infected with HIV as well. A local study at Rawalakot on hematological side effects of pegIFN and ribavirin found that the mean Hb and TLC kept on decreasing until 3 months and PLT until 4 months and then improved. [19]

Discontinuation of treatment in CHC patients due to severe adverse effects in clinical trials was 1 % in sofosbuvir plus RBV groups and 2% in sofosbuvir plus pegIFN and RBV groups. [17] In our study there was not a single patient who discontinued treatment due to severe side effects. This clearly shows the safety profile of sofosbuvir and ribavirin combination as compared to pegylated interferon and ribavirin treatment.

In our study 4 (3.4%) patients had a drop in hemoglobin to less than 10 g/dL, but none had hemoglobin less than 8.5 g/dL. This was similar to another study where four patients, all in the 24-week sofosbuvir plus RBV group, had at least one hemoglobin level of <10g/dL, but none had hemoglobin <8.5g/dL.[18]

The above discussion clearly depicts that sofosbuvir and ribavirin combination is much safer than the pegIFN plus ribavirin or sofosbuvir plus pegIFN and ribavirin combination. Our study had few limitations. We had a small sample size and our sampling method was non-probability sampling.

CONCLUSION

Hematological abnormalities such as a decrease in hemoglobin, leukocytes and platelets are quite uncommon and mild in sofosbuvir and ribavirin therapy, as compared to Interferon based combination therapies.

Author's Contribution:

Concept & Design of Study: Waseem Sarwar Malghani
Drafting: Anum Khakwani
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Revisiting Critically: Asma Tameez ud Din
Final Approval of version: Waseem Sarwar Malghani

Conflict of Interest: The study has no conflict of interest to declare by any author.

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