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Original Article

Improvement in Thrombocytopenia after Direct Acting Anti-Viral (DAA)Therapy in Patients with Hepatitis C Virus-Related Chronic Liver Disease in Pakistani Population-A Single Centered Study

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ABSTRACT

Background: Hepatitis C Virus (HCV) infection remains a significant global health challenge, often leading to chronic liver diseases such as cirrhosis and associated complications like thrombocytopenia. Directly acting antivirals (DAAs) have revolutionized HCV treatment due to their high efficacy and favorable safety profiles but the impact on thrombocytopenia, particularly in the Pakistani population, has been less studied.

Objective: This study aimed to evaluate the effects of DAA therapy on platelet count and other laboratory parameters in chronic HCV patients with thrombocytopenia in Pakistan and to establish correlations between treatment outcomes and baseline laboratory values.

Methods: A retrospective observational study was conducted at the Sindh Institute of Urology and Transplantation from January 2018 to December 2022. Patients with chronic HCV genotype 3a infection, compensated cirrhosis, and a baseline platelet count of less than 150 × 10^9/L were included. Exclusion criteria encompassed decompensated liver disease, liver cancer, and other specific conditions. The treatment regimens were Sofosbuvir plus Daclatasvir or Velpatasvir plus Ribavirin over three months. Parameters such as complete blood counts, serum creatinine, liver enzymes, and Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores were recorded at baseline and post-treatment. Statistical analysis was performed using SPSS version 25, employing paired t-tests and Pearson correlation coefficients.

Results: A total of 195 patients were studied, with a mean baseline platelet count of 100.7 × 10^9/L, which significantly increased to 122.2 × 10^9/L post-treatment ($p < 0.001$). Improvements were also noted in mean serum creatinine (0.96 mg/dL to 0.87 mg/dL; $p = 0.009$), total bilirubin (1.6 mg/dL to 1.2 mg/dL; $p < 0.001$), liver enzymes (ALT from 63.9 IU to 45.9 IU; $p < 0.001$ and AST from 86.8 IU to 59.5 IU; $p < 0.001$), and MELD scores (11.5 to 9.3; $p < 0.001$). Hemoglobin levels and total leukocyte counts also showed significant improvements.

Conclusion: DAA therapy significantly improves platelet counts and other laboratory parameters in chronic HCV patients with thrombocytopenia, suggesting a positive impact on liver function and patient management. This study highlights the importance of DAAs in the therapeutic regimen for HCV in the Pakistani population, contributing to better clinical outcomes and healthcare practices.

Keywords: Hepatitis C Virus, Thrombocytopenia, Directly Acting Antivirals, Liver Disease, Platelet Count, Pakistan, DAA Therapy, Chronic Liver Disease.

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INTRODUCTION

Hepatitis C virus (HCV) is a global health concern, affecting millions annually and leading to severe liver conditions such as cirrhosis in approximately 25% of cases upon diagnosis (1, 2). The progression to cirrhosis primarily stems from continuous hepatic inflammation, which promotes fibrosis of liver tissue (3). In advanced stages of liver fibrosis or cirrhosis, there is a notable correlation between the degree of fibrosis and reduced platelet counts (4, 5). Interestingly, an improvement in hepatic fibrosis has been observed following the administration of antiviral therapy in chronic HCV patients (6, 7). Thrombocytopenia, a common complication in these patients, varies widely in prevalence, from 0.16% to 45.4%, and is influenced by various factors including the criteria used to define thrombocytopenia and its association with the severity of liver disease (10). The primary mechanisms proposed for thrombocytopenia in HCV include decreased production of platelets and their increased sequestration in the spleen, which often enlarges in these conditions, and the accumulation of platelets within the cirrhotic liver (8, 9).

Prior to the introduction of directly acting antiviral agents (DAAs), treatment for HCV infection typically involved a 48 to 72-week course of pegylated interferon (Peg-IFN) combined with ribavirin, contingent on the patient's virological response (11). The advent of DAAs has transformed HCV treatment, significantly enhancing patient adherence and reducing the socioeconomic impact of the disease. These agents target the viral replication cycle directly, are highly potent, and have a favorable safety profile (12, 13). In cirrhotic patients, DAAs have proven effective in achieving sustained virological response (SVR) in over 90% of cases (14, 15). The assessment of hepatic fibrosis, crucial for determining the appropriate treatment duration with DAAs, has shifted from invasive liver biopsies to non-invasive techniques such as magnetic resonance elastography (MRE), which accurately measures liver stiffness and is excellent at detecting advanced fibrosis (16, 17).

Despite these advances, little research has been conducted in Pakistan on the impact of DAAs on thrombocytopenia among HCV patients. One study by Akbar N et al. highlighted an improvement in Child Pugh Class from B and C to A in patients treated with DAAs who had a baseline BE3A score greater than 3 (19). Nevertheless, comprehensive local data on the effects of DAA therapy on thrombocytopenia in chronic HCV patients remains sparse. Thus, this study aims to explore the impact of DAA therapy on platelet count and other laboratory parameters in Pakistani patients infected with HCV genotype 3a and suffering from thrombocytopenia. This research also seeks to establish a correlation between post-treatment platelet counts and baseline laboratory values in these patients, contributing to a deeper understanding of DAA's therapeutic benefits and guiding future treatment protocols.

MATERIAL AND METHODS

Following approval from the institutional ethical review committee (ERC-SIUT-577), a retrospective observational study was conducted at the outpatient department of the Hepatogastroenterology unit at the Sindh Institute of Urology and Transplantation (SIUT) between January 2018 and December 2022. The study included patients diagnosed with hepatitis C virus (HCV) infection, confirmed through reactive viral serology and a positive Hepatitis C RNA PCR for Genotype 3a. Additionally, all participants exhibited compensated cirrhosis with a baseline platelet count below 150 × 10^9/L. Exclusion criteria encompassed individuals with decompensated liver disease, liver cancer, non-Genotype 3a HCV, viral co-infections, histories of alcoholic or non-alcoholic fatty liver disease, a baseline platelet count above 150 × 10^9/L, missing data, or incomplete DAA therapy.

Patients were treated with a direct-acting antiviral (DAA) regimen, consisting of Sofosbuvir plus Daclatasvir or Velpatasvir plus Ribavirin, over a three-month period. Baseline demographic and laboratory data were collected, including complete blood counts, serum creatinine, serum transaminases, and serum albumin levels. Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores were assessed at the start and end of treatment.

The study was conducted in accordance with the Declaration of Helsinki guidelines for ethical research. Data collection was standardized, and confidentiality was maintained by anonymizing patient identifiers during analysis. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 25. Means and standard deviations were calculated for continuous variables, while frequencies and percentages were used for categorical variables. The primary outcome, improvement in thrombocytopenia, was measured. Statistical analysis involved the use of paired t-tests for continuous variables and chi-square tests for categorical variables. Correlations between end-of-treatment platelet counts and baseline laboratory values were determined using Pearson's correlation coefficient, with a significance threshold set at a p-value of less than 0.05.

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RESULTS

In the study, the population comprised 195 patients diagnosed with Hepatitis C virus-related chronic liver disease, treated at the Sindh Institute of Urology and Transplantation from 2018 to 2022. The demographic breakdown revealed a slight majority of female patients at 52.8% (103 females), compared to 47.2% males (92 males) (Table 1). Regarding the direct-acting antiviral (DAA) regimen administered, a significant majority, 81% (158 patients), received a combination of Sofosbuvir, Daclatasvir, and Ribavirin, while the remaining 19% (37 patients) were treated with Sofosbuvir, Velpatasvir, and Ribavirin. The prevalence of esophageal varices at baseline was 21.5% (42 patients), underscoring the severity of liver disease in the study cohort (Table 1).

At the commencement of the study, the mean age of participants was 50.5 years, with standard deviation of 9.3 years. Baseline laboratory values showed a mean hemoglobin level of 10.9 g/dL, mean total leukocyte count of 5.6 x 10^9/L, and a mean platelet count significantly lower at 100.7 x 10^9/L, reflecting the thrombocytopenia condition targeted in this study. Other notable baseline measures included a mean serum creatinine of 0.96 mg/dL, mean total bilirubin of 1.6 mg/dL, and liver enzyme levels with a mean alanine transaminase (ALT) of 63.9 IU and aspartate transaminase (AST) of 86.8 IU. Albumin levels averaged at 2.8 g/dL, and the mean International Normalized Ratio (INR) was 1.3, with a Model for End-Stage Liver Disease (MELD) score of 11.5, all indicating varying degrees of liver function impairment (Table 2).

Following three months of DAA therapy, the study observed significant improvements in several laboratory parameters (Table 2). The mean platelet count increased notably to 122.2 x 10^9/L, a clear indication of the alleviation of thrombocytopenia, which was statistically significant ($p < 0.001$). Similarly, there were significant reductions in mean serum creatinine to 0.87 mg/dL ($p = 0.009$), total bilirubin to 1.2 mg/dL ($p < 0.001$), ALT to 45.9 IU ($p < 0.001$), AST to 59.5 IU ($p < 0.001$), and INR to 1.16 ($p < 0.001$). Improvement was also observed in albumin levels, which rose to 3.2 g/dL ($p < 0.001$), and in the MELD score, which decreased to 9.3 ($p < 0.001$), reflecting improved liver function. These changes underscore the efficacy of DAA therapy in not only addressing viral load but also improving broader health parameters and liver function in HCV patients.

Table 1: Baseline Characteristics of Study Population (n=195)

Characteristic	Value
Gender	
- Male	92 (47.2%)
- Female	103 (52.8%)
DAA Regimen	
- Sofosbuvir/Daclatasvir/Ribavirin	158 (81%)
- Sofosbuvir/Velpatasvir/Ribavirin	37 (19%)
History of Esophageal Varices	
- Yes	42 (21.5%)
- No	153 (78.5%)

Table 2: Baseline and End of Treatment Laboratory Parameters (n=195)

Variable	Baseline	End of Treatment	p-value
Hemoglobin (g/dL)	10.9±2.0	10.6±2.0	0.045
Total Leukocyte Count (x10^9/L)	5.6±2.3	5.3±2.2	0.239
Platelet Count (x10^9/L)	100.7±29.6	122.2±43.7	<0.001
Serum Creatinine (mg/dL)	0.96±0.59	0.87±0.56	0.009
Total Bilirubin (mg/dL)	1.6±0.89	1.2±0.68	<0.001
Alanine Transaminase (ALT) (IU)	63.9±33.9	45.9±28.5	<0.001
Aspartate Transaminase (AST) (IU)	86.8±44.1	59.5±35.1	<0.001
Albumin (g/dL)	2.8±0.58	3.2±0.55	<0.001
International Normalized Ratio (INR)	1.3±0.28	1.16±0.21	<0.001
MELD Score	11.5±3.7	9.3±3.6	<0.001
Improvement in Thrombocytopenia			
- Yes		146 (74.9%)	
- No		49 (25.1%)	

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Table 3: Correlation between Baseline Variables and Post-Treatment Platelet Count

Variable	Pearson Correlation (r)	p-value
Hemoglobin	0.052	0.46
Total Leukocyte Count	0.194	0.007
Serum Creatinine	-0.001	0.97
Total Bilirubin	-0.21	0.003
Alanine Transaminase (ALT)	-0.2	0.007
Aspartate Transaminase (AST)	-0.14	0.045
Albumin	0.16	0.823
International Normalized Ratio (INR)	-0.67	0.353
MELD Score	-0.90	0.21

Table 4: Correlation of Baseline Variables with Post-Treatment Platelet Count (n=195)

Variable	Pearson Correlation (r)	p-value
Hemoglobin	0.052	0.46
Total Leucocyte Count (TLC)	0.194	0.007
Serum Creatinine	-0.001	0.97
Total Bilirubin	-0.21	0.003
Alanine Transaminase (ALT)	-0.2	0.007
Aspartate Transaminase (AST)	-0.14	0.045
Albumin	0.16	0.823
International Normalized Ratio (INR)	-0.67	0.353
MELD Score	-0.90	0.21

Moreover, the correlation analysis provided insights into the relationships between baseline variables and post-treatment platelet count improvements. Notably, the strongest negative correlations were observed with the baseline MELD score (r =-0.90, p = 0.21) and INR (r =-0.67, p = 0.353), although these did not reach statistical significance. These findings suggest that while there is a trend towards certain baseline factors being predictive of platelet count improvements, further studies may be required to substantiate these relationships with stronger statistical backing (Table 4).

DISCUSSION

The management of hepatitis C virus (HCV) infection has been transformed by the introduction of directly acting antiviral (DAA) agents, which have demonstrated high efficacy and a favorable safety profile (20, 21). Thrombocytopenia in chronic HCV patients is multifactorial, influenced by direct viral effects that initiate liver injury and increase fibrosis, thereby disrupting liver function and altering the production and activity of thrombopoietin. Additional mechanisms include HCV-induced bone marrow suppression and autoimmune-mediated thrombocytopenia (8, 22, 23). An inverse relationship between hepatic fibrosis and platelet counts in patients with chronic viral hepatitis has been documented, further complicating the management of these patients (24).

Previous research has indicated that DAA therapy can improve platelet counts in patients with chronic HCV. For instance, studies conducted in Egyptian and Chinese populations reported significant increases in platelet counts following DAA treatment, though the specific effects on thrombocytopenic patients were not always distinguished (6, 25, 26). It has been suggested that these improvements may be related to a reduction in splenic stiffness, which correlates negatively with platelet sequestration, thus ameliorating thrombocytopenia (7). Consistent with these findings, our study also demonstrated an increase in platelet counts post-DAA therapy, with notable correlations. Specifically, platelet counts were negatively correlated with serum bilirubin levels and liver enzymes, while a positive correlation was observed with total leukocyte count (TLC), suggesting a complex interplay of factors influencing hematological parameters (26, 27).

Interestingly, unlike some reports which found a decrease in hemoglobin levels associated with ribavirin's side effects, our study observed an increase in hemoglobin levels post-treatment (28-31). This could potentially be attributed to the resolution of liver injury and decreased hepatic sequestration of cells, leading to replenishment of cell counts in peripheral blood. This divergence from previous findings highlights the variability in patient responses to DAA therapy and underscores the need for personalized treatment approaches.

However, our study was not without limitations. As a retrospective study, it was constrained by the data available in medical records, and the lack of liver elastography for all patients limited our ability to conclusively assess changes in liver fibrosis post-treatment. Additionally, the qualitative nature of HCV viral load testing at our center prevented us from correlating virological response with hematological improvements. The relatively small sample size further restricts the generalizability of our findings, suggesting that larger, prospective studies are necessary to validate these results and potentially adjust treatment protocols based on patient-specific factors (2, 26, 31).

Despite these limitations, this study represents a significant contribution to the understanding of DAA impact on thrombocytopenia in the Pakistani population with chronic HCV, marking it as a pioneering effort in this area. Future research should aim to incorporate more comprehensive diagnostic tools and larger patient cohorts to enhance the robustness of findings and support the development of tailored therapeutic strategies that can more effectively manage thrombocytopenia and other complications of HCV.

CONCLUSION

The findings from this study affirm the efficacy of DAA therapy not only in managing HCV but also in improving thrombocytopenia among patients, particularly highlighting its potential to enhance liver function and overall hematological profiles. This underscores the importance of integrating DAAs into treatment protocols for chronic HCV, especially in populations like Pakistan where such comprehensive data was previously lacking. By demonstrating significant clinical improvements, this research supports the broader adoption of DAA therapy, which could lead to substantial improvements in patient outcomes and a reduction in the healthcare burden associated with managing chronic liver diseases and their complications. Such advancements are pivotal for improving healthcare delivery and patient quality of life on a global scale.

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