ORIGINAL ARTICLE

Haematological Disorders: Relative Contraindications for the Commencement of Chronic HCV Treatment, Otherwise Eligible for Antiviral Therapy

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ABSTRACT

Background: European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Disease (AASLD) reported peripheral blood cytopenia as relative contraindications for HCV treatment. It is a potentially limiting factor the commencement and the effect of antiviral therapy in HCV patients

Objective: the present study was planned to rule out peripheral blood cytopenias among chronic HCV infected patients.

Material & Methods: This cross-sectional study was conducted at Hepatitis Clinic, Jinnah Hospital Lahore from 15th august to 30th December 2016. A total of 530 samples were collected from chronic HCV positive patients. Non-probability consecutive sampling technique was used. About 05 ml of blood sample was collected (EDTA + Clotted) from every patient, by using standard venipuncture technique. Every sample was processed in pathology department &Dr. Abdul Qadir Khan PCR lab of JHL. HCV RNA PCR & and peripheral blood count was done from every sample. Data was stratified by age, gender and duration of hepatitis C positivity to deal with effect modifier. Post-stratification chi-square test was used to determine the significance. P-value < 0.05 was taken significant.

Results: Out of total 530 study participants 48.7% (n=258) were males and 51.3% (n=272) were females, Mean age was 40.80 +12.32. Among total 530 HCV-positive patients neutropenia was highly prevalent peripheral blood disorder 17.9% (95% CI 29–60) (95/530): followed Anemia 10.9% (95% CI 9–16) (58/530): and the least frequency of thrombocytopenia was observed in 8.1% (95% CI 83000–123000) (43/530) patients.

Conclusion: We conclude that unexplained neutropenia/thrombocytopenia/ anemia, should be tested for HCV infection. There is may be of association of HCV and peripheral blood cytopenias. Therefore to rule the biological basis of these associations further studies are needed.

Keywords: HCV, Anemia, Neutropenia, thrombocytopenia,

Introduction

In spite of multiple solid steps taken to eradicate Hepatitis, still, it is most alarming dilemma around the globe with the incident rate of 3.3% (n=200 million). Globally every year 0.2- 40% peoples are victimized by this bug. Being low-to-middle-income country, unfortunately, Pakistan ranked 2nd high burden country for hepatitis with incident rate of 4.5% -8%.

European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Disease (AASLD) guidelines suggested that peripheral blood cytopenia as relative contraindications for HCV treatment.[1, 2] Its relevance is a factor potentially limiting the commencement and the effect of antiviral therapy in HCV patients remains unknown up to now.

Hepatitis C virus (HCV) infection refers to the presence of clinical signs or symptoms of hepatitis within six months of presumed HCV exposure. While acute hepatitis C virus (HCV) infection is estimated to account for 15 percent of symptomatic cases of the acute liver disease, the majority of patients with acute HCV go undetected. This is due in large part to the fact that patients with acute HCV are typically asymptomatic. According to the Centers for Disease Control (CDC) and Prevention estimated that there were 17,000 new cases of HCV in 2010, but that only 2800 patients (16 percent) presented with symptoms of acute hepatitis Acute hepatitis typically develops 2 to 26 weeks after exposure to hepatitis C virus (HCV), with a mean onset of 7 to 8 weeks. [3]

In patients who experience symptoms, the acute illness usually lasts for 2 to 12 weeks. Symptoms may include jaundice, nausea, dark urine, and right upper quadrant pain. However, most patients who are acutely infected with HCV are asymptomatic. Patients with acute HCV typically have moderate transaminase elevations, though they may go undetected in asymptomatic patients. Fulminant hepatic failure due to acute HCV infection is very rare but may be more common in patients with underlying chronic hepatitis B virus infection.

Anemia, neutropenia, leukopenia, and thrombocytopenia are among the numerous side effects of currently available HCV treatments.[4] Preliminary data suggest that the infection itself can also induce autoimmune hemolytic anemia, leukopenia, and thrombocytopenia.[5] These complications can influence HCV treatment and adherence, which could compromise outcomes. Although no approved treatments for HCV-related hematologic complications exist.

Evidence of HCV replication also has been reported in peripheral blood cells, and abnormal blood counts have been noted in clinic patients with HCV infection.[6] However, the frequency and severity of peripheral blood cell count abnormalities in the majority of HCV-infected individuals are unknown. No universally accepted normal range exists for most components of the peripheral blood count. In addition, a number of factors are known to affect both the peripheral blood count and the prevalence of HCV infection. Thus, the objective of this investigation was to evaluate the frequency and severity of peripheral blood cell abnormalities in HCV-infected patients in the general population after accounting for age, race, and other potential confounding factors.

Methodology

Authors declared no conflict of interest. Study protocols were approved by the ethical board of Jinnah hospital Lahore Pakistan. It was the sectional study conducted at Hepatitis Clinic of Jinnah Hospital Lahore from 15th august to 30th December 2016.HCV positive patients attending Hepatitis clinic of Jinnah hospital Lahore. Inclusion criteria include Male & females with age of 20-60 years. History of HCV positivity from last 6 months**,** Exclusion Criteria include 1) Patients not giving consent to participate in the study, 2) history or already having signs of decompensated liver diseases i.e. cirrhosis, splenomegaly (>15cm) and ascites on ultrasonography. 3) History of any blood disorder like ITP, aplastic anemia, vitamin B12 deficiency. 4) History of any autoimmune disease or infection affecting cell line i.e. SLE, malaria, dengue, typhoid, cancer. 5) Already taking interferon therapy for the disease. History of drug intake causing blood cell lines disturbances in last 6 months like phenytoin, carbimazole. Nonprobability consecutive sampling technique was used; the Sample size of 530 cases was calculated with 95% confidence level, 1.5 % margin of error. Informed consent: An informed consent was taken from every participant. Standard venipuncture technique was used to collect the blood sample. About 05 ml of blood sample was collected from every participant by venipuncture technique in two purple top vacutainers. One sample (EDTA) of every patient was sent to pathology department and second to Dr. Abdul Qadir Khan PCR lab of JHL for further analysis. Every test was performed by highly skilled Medical Lab Technologist/Hematologist and molecular biologist. Every sample was processed according to standard guidelines following parameters were calculated,

Confidentiality of the results was ensured. (1) HCV RNA PCR by using (Cepheid smart cycler® II Real-time PCR) (2) White blood cells (WBC) count by using Xp-100 Sysmex hematology analyzers.(3) Hemoglobin (HB) levels by using Xp-100 Sysmex hematology analyzers.(4) Platelets count by using Xp-100 Sysmex hematology and microscopic examination of peripheral smear (5) Absolute Neutrophils count by using Xp-100 Sysmex hematology and analyzer microscopic examination of peripheral smear.

Data Analysis: Statistically analysis was made using a statistical package of social services (SPSS) version 17.0. Qualitative variables like sex, abnormalities of blood counts (Anemia, neutropenia, and thrombocytopenia) and quantitative variables like age were also calculated. Peripheral blood cytopenias were calculated according to following protocols.(1) Anemia: Hemoglobin levels < 12 g/dl in females and <13 g/dl in males. (2) Thrombocytopenia: platelet count <100,000 mm3.(3) Neutropenia: Absolute neutrophil count less than 1500 cell/mm3. Data was stratified by age, gender and duration of hepatitis C to deal with effect modifier. Post-stratification chi-square test was used to determine the significance. P-value < 0.05 was taken significant.

The decision to treat a patient with chronic HCV infection is based on several factors, including the natural history of the disease, the stage of fibrosis, and the efficacy and adverse effects related to therapy. Therapy is generally considered appropriate for patients who (1) Are >18 years of age (2) Have HCV RNA detectable in the serum (3) Have a liver biopsy with chronic hepatitis and significant fibrosis (4) Have compensated liver disease (5) Have acceptable hematologic and biochemical indices (6) Are willing to be treated and conform to treatment requirements (7) Have no contraindications to treatment. Additional factors such as alcohol use, drug use, chronic kidney disease, or prior liver transplantation are also taken into account when deciding whether to start a patient on antiviral therapy

Results

Out of total 530 study participants 48.7% (n=258) were males and 51.3% (n=272) were females. Mean age 40.80 ±12.32. **Figure:1**

Among total 530 HCV patients neutropenia was highly prevalent disorder 17.9% (95% CI 29–60) (95/530): followed Anemia 10.9% (95% CI 9–16) (58/530): and least frequency of thrombocytopenia was observed in 8.1% (95% CI 83000–123000) (43/530):**Figure:2**

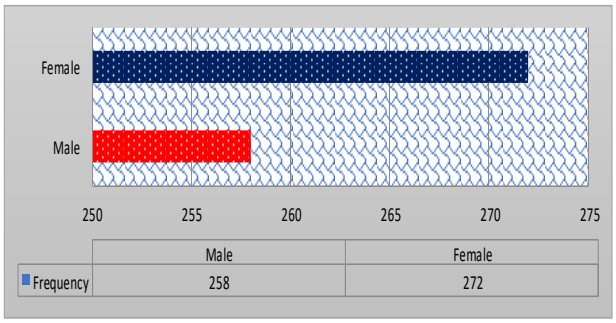

Figure:1 Gender-based frequency distribution of HCV positive study participants

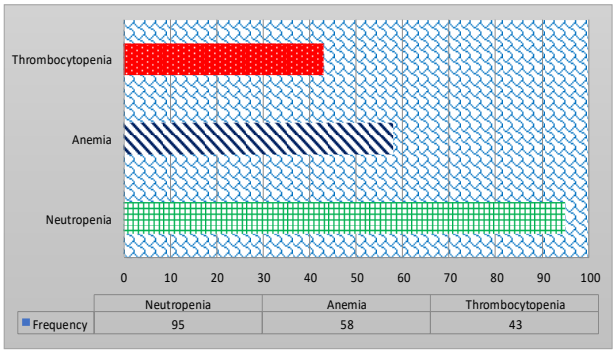

Figure:2 Frequency distribution of peripheral blood disorders in study population (n=530)

Mean for the duration of HCV positivity was 10.90 ±3.76 months, for hemoglobin levels mean was 14.34 ± 1.58, g/dl. For WBC count it was 4876.42 ± 1533.59 g/dL, for neutrophils 49.42 ± 6.23 percent. Among band cells mean was observed 3.84 ± .88 percent. Mean for Absolute neutrophils count (ANC) was 2596.06 ± 790.95 /mm^3. In the case of platelet count mean was 109147.17 ± 8354.9 /mm^3.

Table:1 showed that out of 530 HCV positive subjects 10.9% (95% CI 58/530): were suffering from anemia includes males 55.1% (95% CI 32/58) and females 44.8% (95% CI 26/58) there was no significant association between genders (P-value=0.294). Age group wise distribution showed 55.1% (95% CI 32/58) in 20-40 years, and among 41-60 years it was 44.8% (95% CI 26/58) there was no significant association between genders(P-value=0.404).Duration of HCV positivity was also ruled out and observed that among < 01 years group, almost 53.4% (95% CI 31/58) were anemic while in >01-year group 46.5%(95% CI 27/58) were anemic with the non-significant association (P-value=0.125)

Table I: Group wise distribution and statistics of anemia						
Groups		Anemia		Total	Chi-Square	P. Value
Gender		Present	Absent			
	Male	32	226	258	1.099	0.294
	Female	26	246	272		
	Total	58	472	530		
Age group	20-40	26	239	265	0.697	0.404
	41-60	32	233	265		
	Total	58	472	530		
Duration of HCV positivity	<01 year	31	301	332	2.352	0.125
	>01year	27	171	198		
	Total	58	472	530		

Table II: Group wise distribution and statistics of Neutropenia						
Groups		Neutropenia		Total	Chi-Square	P. Value
Gender		Present	Absent			
	Male	50	208	258	0.724	0.395
	Female	45	227	272		
	Total	95	435	530		
Age group	20-40	56	209	265	3.706	0.054
	41-60	39	226	265		
	Total	95	435	530		
Duration of HCV positivity	<01 year	58	274	332	0.724	0.125
	>01year	37	161	198		
	Total	95	435	530		

Table II showed that out of 530 HCV positive subjects 17.9% (95% CI 95/530):were suffering from neutropenia include males 52.6% (95% CI 50/95) and females 47.3% (95% CI 45/95) with non-significant association between genders (P-value=0.395). Age group based distribution showed 58.9% (95% CI 56/95) in 20-40 years, and among 41-60 years it was 41.0% (95% CI 39/95) with non-significant association (P-value=0.054). Duration of HCV positivity was also ruled out and observed that among < 01 years group, almost 61.0% (95% CI 58/95) were suffered in neutropenia while in >01-year group were 38.9%(95% CI 37/95) with the non-significant association (P-value=0.125)

Table III showed that out of 530 HCV positive subjects 8.1% (95% CI 43/530): were suffering from thrombocytopenia include males 23.2% (95% CI 10/43) and females 76.7% (95% CI 33/43) with significant association (P-value=0.001). Age group based distribution showed 51.1% (95% CI 22/43) in 20-40 years, and among 41-60 years it was 48.8% (95% CI 21/43) with the non-significant association (P-value=0.874). Duration of HCV positivity was also ruled out and observed that among < 01 years group, almost 74.4% (95% CI 32/43) were suffered in neutropenia while in >01-year group were 25.5%(95% CI 11/43) with the non-significant association (P-value=0.096)

Table:3 Group wise distribution and statistics of Thrombocytopenia						
Groups		Thrombocytopenia		Total	Chi-Square	P. Value
Gender		**Present**	**Absent**			
	Male	10	248	258	12.107	0.001
	Female	33	239	272		
	Total	43	487	530		
Age group	20-40	22	243	265	0.025	0.874
	41-60	21	244	265		
	Total	43	487	530		
Duration of HCV positivity	<01 year	32	300	332	2.774	0.096
	>01year	11	187	198		
	Total	43	487	530		

Discussion

HCV positive chronic liver disease (CLD) patients are frequently present with peripheral blood cytopenias.[5] Multiple pathophysiological mechanisms are accountable for the commencement of these disorders like anemia, neutropenia, and thrombocytopenia. Pre-treatment presence of peripheral blood disorders may limit the suitability of patients for antiviral therapy against HCV because pegylated interferon and ribavirin therapies are significantly associated with myelosuppression and hemolysis. [7, 8]

According to present study, out of 530 HCV-infected patients neutropenia was highly prevalent 17.9% (95% CI 29–60) (95/530): followed anemia 10.9% (95% CI 9–16) (58/530): and the least frequency of thrombocytopenia was observed in 8.1% (95% CI 83000–123000) (43/530).

Our study reported high prevalence of peripheral blood disorder with high rate of neutropenia as compare to the previous study, by Giannini et al [9] reported, out of 3059 HCV patients, 49.7% were-were not eligible for HCV treatment according to EASL guidelines, due to presence of clinically significant co-morbidities 31.8%, decompensated liver disease and/or hepatocellular carcinoma 7.6%, or advanced age >75 years 10.3%. Out of remaining 1,538 patients almost 15.1% were rejected due to any peripheral blood disorder. Particularly, anemia 8.9% (n=137), while thrombocytopenia 6.5% (n=100) and neutropenia in 3.2% (n=48).

Another study mentioned that HCV positive patients are 3-fold more likely to have neutropenia (HCV positive, 9% vs. HCV negative, 3%, P<.0001) and 2.6-fold more likely to have thrombocytopenia (HCV positive, 13% vs. HCV negative, 5%, P < .0001). HCV infection was observed >20% neutropenia or thrombocytopenia patients. Similar to present study There was also no association between HCV status and anemia.[5]

On another side, a retrospective study by Roomer et al [10] contradicts with the present study and multiple previous studies that, HCV treatment with peginterferon and ribavirin was harmless in patients with pre-treatment thrombocytopenia and therefore these patients should not be excluded from antiviral therapy against HCV.

However, in Giannini cohort, thrombocytopenia with as highly prevalent peripheral blood disorder as the factor of treatment discontinuation. A proof-of-concept study previously exhibited that administration of eltrombopag, an orally available thrombopoietin receptor agonist was successfully able to securely upsurge platelet count in HCV patients with thrombocytopenia and permits commencement of antiviral treatment against HCV. [11]

The present study reported 17.9% (95% CI 29–60) (95/530) neutropenia conversely, its clinical significance necessitates further exploration. While some reported directed in advanced cirrhosis patients, established that antiviral therapy may be linked to life-threatening infections. [12, 13] Again on-other hand a retrospective report carried out in HCV patients with less advanced disease exhibited that occurrence of neutropenia during HCV treatment with peg-interferon and ribavirin does not appear to link with any bacterial infections. [10]

Another study of the reported a treatment-experienced among genotype 1 cirrhotic individuals retreated by triple regimen with either boceprevir or telaprevir, as result grade 3/4 neutropenia was noticed in 4.7% among Telaprevir treated patients and 5% of boceprevir-treated patients.[14] However, in this study grade, 3/4 infections were noticed in 8.8% of telaprevir-treated patients 2.5% among boceprevir-treated patients. Moreover, out of the eight deaths, five were because of bacterial infections. Therefore, attentiveness is recommended in the treatment of neutropenia, even if infection did not appear to be related with neutropenia. The literature showed multiple factors that could have confounded or modified the linkage of HCV infection with neutrophil and platelet counts.[15] Previous studies suggested that HCV could cause thrombocytopenia via the autoimmune process.[6] Tactlessly, as liver and bone marrow biopsy samples are not obtained, additional researches should be done to rule out a biologic basis for these associations. It is exciting to communicate that neutropenia and thrombocytopenia are concomitant with some markers of undecorated liver disease like elevated serum globulin or bilirubin levels or low albumin levels.[16]

Conclusion

Pre-treatment presence of peripheral blood disorders may limit the suitability of patients for antiviral therapy against HCV, therefore the patients with unexplained neutropenia/thrombocytopenia/ anemia should be tested for HCV infection. There is may be an association of these peripheral blood cytopenias with chronic hepatitis C further studies are required to rule the biological basis of these associations.

Limitations: it is hospital based study,

References

1. Liver EAFTSOT. EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. Journal of hepatology. 2012;56(4):908-43.

2. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49(4):1335-74.
3. Westbrook RH, Dusheiko G. Natural history of hepatitis C. Journal of hepatology. 2014;61(1):S58-S68.
4. Zeuzem S, Buti M, Ferenci P, Sperl J, Horsmans Y, Cianciara J, et al. Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. Journal of hepatology. 2006;44(1):97-103.
5. Streiff MB, Mehta S, Thomas DL. Peripheral blood count abnormalities among patients with hepatitis C in the United States. Hepatology. 2002;35(4):947-52.
6. Cacoub P, Renou C, Rosenthal E, Cohen P, Loury I, Loustaud-Ratti V, et al. Extrahepatic Manifestations Associated with Hepatitis C Virus Infection: A Prospective Multicenter Study of 321 Patients. Medicine. 2000;79(1):47-56.
7. Schmid M, Kreil A, Jessner W, Homoncik M, Datz C, Gangl A, et al. Suppression of haematopoiesis during therapy of chronic hepatitis C with different interferon α mono and combination therapy regimens. Gut. 2005;54(7):1014-20.
8. Sulkowski MS. Management of the hematologic complications of hepatitis C therapy. Clinics in liver disease. 2005;9(4):601-16.
9. Giannini EG, Marenco S, Fazio V, Pieri G, Savarino V, Picciotto A. Peripheral blood cytopaenia limiting initiation of treatment in chronic hepatitis C patients otherwise eligible for antiviral therapy. Liver International. 2012;32(7):1113-9.
10. Roomer R, Hansen BE, Janssen HL, de Knegt RJ. Thrombocytopenia and the risk of bleeding during treatment with peginterferon alfa and ribavirin for chronic hepatitis C. Journal of hepatology. 2010;53(3):455-9.
11. McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, Bourliere M, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. New England Journal of Medicine. 2007;357(22):2227-36.
12. Iacobellis A, Siciliano M, Perri F, Annicchiarico BE, Leandro G, Caruso N, et al. Peginterferon alfa-2b and ribavirin in patients with hepatitis C virus and decompensated cirrhosis: a controlled study. Journal of hepatology. 2007;46(2):206-12.
13. Annicchiarico B, Siciliano M, Avolio A, Caracciolo G, Gasbarrini A, Agnes S, et al., editors. Treatment of chronic hepatitis C virus infection with pegylated interferon and ribavirin in cirrhotic patients awaiting liver transplantation. Transplantation proceedings; 2008: Elsevier.
14. Hezode C, Dorival C, Zoulim F, Poynard T, Mathurin P, Pol S, et al. 8 SAFETY OF TELAPREVIR OR BOCEPREVIR IN COMBINATION WITH PEGINTERFERON ALFA/RIBAVIRIN, IN CIRRHOTIC NON RESPONDERS. FIRST RESULTS OF THE FRENCH EARLY ACCESS PROGRAM (ANRS CO20-CUPIC). Journal of Hepatology. 2012;56:S4.
15. Schwartz J, Weiss ST. Cigarette smoking and peripheral blood leukocyte differentials. Annals of epidemiology. 1994;4(3):236-42.
16. Bashour FN, Teran JC, Mullen KD. Prevalence of peripheral blood cytopenias (hypersplenism) in patients with nonalcoholic chronic liver disease. The American journal of gastroenterology. 2000;95(10):2936-9.