

Role of Eltrombopag in treatment of thrombocytopenia associated with chronic Hepatitis C Virus

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Background: Thrombocytopenia is a common hematological abnormality observed in patients infected with hepatitis C virus (HCV). Thrombocytopenia is a well-known relative contraindication for the initiation of antiviral therapy in HCV-infected patients and may also result in the postponement of many invasive procedures that chronic liver disease (CLD) patients may need to undergo. This study aiming to determine the platelet response to eltrombopag and side effects of eltrombopag therapy in patients with HCV-associated thrombocytopenia.

Patients and methods: This prospective study was carried out on 30 patients with chronic HCV-associated thrombocytopenia ($<50,000 \times 10^9/L$) that precludes the initiation of HCV therapy. Eltrombopag was initiated at a dose of 25 mg once daily; the dose was adjusted with 25 mg increments every 2 weeks to achieve the target platelet count. The primary end point was to achieve stable target platelet count ($>100,000 \times 10^9/L$) required to initiate antiviral therapy and any surgical intervention.

Results: Treatment response was achieved in 29 (96.7%) patients. This prospective study showed that when the dependent variable was the increased platelet count at second week of treatment while the independent variables are: age, albumin level, gender, platelet count before treatment, AST, and WBC count. The only significant positive predictive factor was the platelet count before treatment.

Conclusion: Eltrombopag causes significant elevation of platelet count in patients with HCV related thrombocytopenia, so that Eltrombopag could be used prior to and during treatment with antiviral therapy when thrombocytopenia become confronting problem as well as before surgical interventions.

Keywords: HCV, eltrombopag therapy, thrombocytopenia.

Introduction:

Thrombocytopenia is a well-known relative contraindication for the initiation of antiviral therapy in HCV-infected patients and may also result in the postponement of many invasive procedures that chronic liver disease (CLD) patients may need to undergo, such as percutaneous, transjugular, or laparoscopic liver biopsy; paracentesis; thoracentesis; radiofrequency ablation; or partial hepatectomy for hepatocellular carcinoma. The latter group of patients may also need to undergo splenectomy, especially if the platelet counts are $<50,000/mm^3$ (Cacoub et al., 2000).

Different therapeutic strategies have been suggested and tried for the treatment of HCV-related thrombocytopenia in different studies with variable success (generally disappointing). However, the recent introduction of second-generation thrombopoietin receptor agonists (TPO-RAs) has opened up a novel way to treat thrombocytopenia. In 2008, the US Food and Drug Administration approved two TPO-RAs – eltrombopag and romiplostim – for use in chronic immune thrombocytopenic purpura (CITP) patients refractory to at least one standard treatment (Nurden et al., 2009).

It appears that it is an efficacious treatment modality for the short-term amelioration of thrombocytopenia. There are some relatively serious safety concerns related to the use of this drug in CLD patients, particularly treatment-related thrombosis. It does not appear to be a safe alternative to repeated platelet transfusions in CLD patients undergoing an invasive procedure. This drug should normally be used for short-term periods of ~2 weeks and at the lowest possible effective dose (Tarantino et al.,2013).

Patients and methods:

This prospective study was conducted at the departments of internal medicine , Qena University Hospitals, in the period between December 2018 till September 2019. The study was carried out on 30 patients with chronic HCV-associated thrombocytopenia (platelet count $<50,000 \times 10^9/L$) that precludes the initiation of HCV therapy. The patients were divided into two groups (responders and nonresponders) according to their response to eltrombopag.

This study was conducted in accordance with the guidelines of the Declaration of Helsinki (1975) and its subsequent amendments (1983). Written informed consent was obtained from all patients prior to the study after full explanation of benefits and risks of the study.

This study was approved by the Qena University Faculty of Medicine research ethical committee. Full medical history was obtained from the patients, and a thorough clinical examination was conducted for each patient.

Laboratory and other assessments:

1. Complete blood count including hemoglobin level, total leukocytic count, and platelet count (automatic blood cell counter model PCE-210N; Erma Inc) was evaluated.
2. Liver function tests (alanine transaminase, aspartate transaminase,

serum bilirubin, serum albumin, and international normalized ratio) were performed.

3. HCV-RNA PCR assay was carried out by real-time PCR using Step One instrument and software (Applied Biosystems).

4. Abdominal ultrasonography was conducted (splenomegaly and huge splenomegaly were considered if the splenic span was .13 and 20 cm, respectively). (Tchelepi et al.,2002).

5. Child–Pugh score was calculated for the assessment of liver status in cirrhotic patients.(Pugh et al.,1973).Eltrombopag was initiated at a dose of 25 mg once daily. The dose was adjusted with 25 mg increments every 2 weeks – when needed – to achieve the stable target platelet count ($>100,000 \times 10^9/L$) required to initiate antiviral therapy. Dose reduction by 25 mg was considered if platelet counts were in the range of $101,000–150,000 \times 10^9/L$. The maximum dose of eltrombopag was 100 mg once daily. Nonresponders were identified as those patients who had received eltrombopag 100 mg/day for 2 weeks and failed to meet the platelets threshold. Complete blood picture and liver function tests were requested once weekly until the target platelet count was maintained for 1 month. Thereafter, monitoring frequency was reduced to once a month.

Statistical analysis:

All patients had been analyzed using Statistical package for Social Sciences (SPSS).

Results:

Thirty patients with chronic HCV-associated thrombocytopenia were enrolled in this study. The mean platelet count of the enrolled patients was $(35.3 \pm 11.1 \times 10^3)/mm^3$.

The Age& laboratory features of the patients.Data are shown in Table (1)

Table (1). Age & laboratory features of the patients.

Variables	mean±SD
Age	54.5±5.3
Hemoglobin	12.5±1.6
WBCS	5.8±2.4
Platelets	35.3±11.1
ALT	29±16.5
AST	32.6±14
Total bilirubin	0.52±0.34
Albumin	3.8±0.36
INR	0.9±0.15

Of the 30 patients enrolled in the study, 4(13.33%) patients reported adverse events as shown in Table (2)

Table 2: Side effect of eltrombopag.

Variable	Number(%)
Headache &fatigue	1(3.3%)
Nausea &diarrhea	2(6.7%)
Thromboembolism	1(3.3%)portal vein thrombosis
Increased bilirubin	0(0%)
Increased transaminases>3 times normal	0(0)
Hepatic decomposition	0(0%)
Death	0(0%)

Eltrombopag response was achieved in 29 (96.7%) patients. The mean duration of treatment with eltrombopag for the responders was 3.89±1.64 weeks, ranging between 2 and 8 weeks, and the mean dose was 48.65±20.18 mg/day, ranging between 25 and 100 mg/day. shown in Table 3.

Table 3: Number of patients reach target platelets count >100.

Time	No (%)
2 weeks	6 (20%)
4	14(46.7%)
6	9(30%)
Total responder	29(96.7%)
Non responder	1(3.3%)

Platelet count was significantly elevated, as at the base line platelet mean was 35±11× 10³/mm³ and after 2 weeks after treatment ,the mean platelet count become 94±16× 10³/mm³ with P-value <0.001 and after 4 weeks post treatment the mean of platelet count become 195±41× 10³/mm³ with P-Value <0.001 .

Table 4: Changes in platelets count from base line and during follow up periods.

variab le	Base line plate lets	2 week s Post treat ment	P 1- val ue	4 week s post treat ment	P 2- val ue
Platele ts count (mean ±SD)	35± 11	94±1 6	<0. 001	195± 41	<0. 001

Table 6: Clinical Characteristics of the patients according to respond to treatment .

Variables	respond to treatment		p- value
	Withi n 1 month	After 1 mont h	
Gender	Mal e	14(70 %) 7(70 %)	1
	Fem ale	6(30%) 3(30 %)	

Liver chihrosis	Yes	9 (45%)	2(20 %)	0.18 0
	No	11(55 %)	8(80 %)	
Splenom egypt	Yes	9(45%)	4(40 %)	0.79 4
	No	11(55 %)	6(60 %)	
Child puch score	5	14(70 %)	8(80 %)	0.71 9
	6	6(30%)	2(20 %)	
Age		53±6	57±3	0.11 2
HGB		12±1. 8	12.4± 1.3	0.62 9
Wbcs		5±2	7±3	0.13 7
Platelets		41±6	24±8	<0.0 01*
ALT		31.7± 19	24±9	0.39 7
AST		4±14	29±1 3	0.30 6
Total bilirubin		0.5±0. 4	0.47± 23	0.89 4
Albumin		3.7±0. 4	3.8±0 .27	0.82 4
INR		1.18± 0.16	1.1±0 .09	0.34 9

ALT, Alanine transaminase; ; INR , International Normalized Ratio

Table (6) : shows that patients are divided into two groups according to their response to treatment within one month and after one month. If we considered patients who respond to treatment within one month as group 1 and patients who respond to treatment after one month as group 2.

So as regard the gender of the patients and liver cirrhosis there was no

significance difference between the two groups, (P-value=1,0.180 respectively). According to presence of the splenomegaly among the patients and ChildPauch Score there was no significance difference between the two groups, (P-value=0.794& 0.719 respectively).

Also, Hemoglobin level had no significant difference between group 1 (12±1.8) and the group 2 (12.4±1.3), (p-value=0.629). White blood cells count was lower in group 1 (5±2) than in group2 (7±3), with no significant difference between the two groups (p-value=0.137). Platelets count was significantly elevated in group 1 by (41±6) more than group 2 (24±8), with significant difference between the two groups (p-value < 0.001).

Alanine transaminase (ALT) level was higher in group 1 (31.7±19) than that in group2 (24±9), with no significant difference between the two groups (p-value=0.397) , Aspartate transaminase (AST) level was lower in group1 (4±14) than that of group 2 (29±13), with no significant difference between the two groups (p-value =0.306) .Total bilirubin level was slightly elevated in group 1 (0.5±0.4) than that in group 2 (4.4±2.5), with no significant difference between the two groups (p-value=0) , and Albumin level was almost the same in group 1 (3.7±0.4) and in group2 (3.8±0.27), with no significant difference between the two groups (p-value =0.824). INR was almost the same in group 1(1.18±0.16) and in group 2 (1.1±0.09), with no significant difference between the two groups (p-value=0.349).

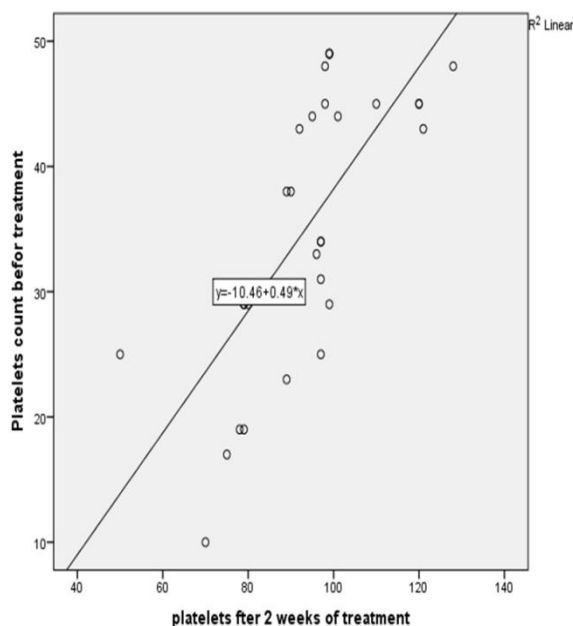


Figure (1) : Correlation coefficient between platelet count after 2 weeks of treatment and platelet count before treatment.

Discussion:

The use of eltrombopag therapy in patients with HCV-associated thrombocytopenia has been reported, (Akahoshi et al.,2014).

Thirty patients with chronic HCV-associated thrombocytopenia with platelet count $<50,000 \times 10^9/L$ were included in this study. The aim was to assess the ability of eltrombopag to increase the platelet count above the threshold ($100 \times 10^9/L$), and thus enable the initiation of antiviral therapy in patients. Eltrombopag response was achieved in 29 (96.7%) patients. The results of our study were slightly better than those of the ENABLE-1 and ENABLE-2 studies. These two studies included 715 and 805 patients with chronic HCV infection, respectively, with a platelet count $75 \times 10^9/L$, and their purpose was to assess the ability of eltrombopag to increase the platelet count above the threshold ($100 \times 10^9/L$) to enable the initiation of interferon

treatment in patients. (Afdhal et al.,2014).

In addition, the response rate in our study was better than that of the ELEVATE study which included 292 patients with chronic liver disease and thrombocytopenia with a platelet count $<50 \times 10^9/L$ before performing elective invasive procedures. Eltrombopag response was achieved in 72% of patients.(Giannini et al.,2014).

The pathogenesis of thrombocytopenia in patients with HCV-associated liver disease is multifactorial rather than involving hypersplenism alone.(Peck-Radosavljevic et al., 2000).

The pathogenesis of thrombocytopenia in patients with chronic liver disease involves reduced thrombopoietin production, spleen sequestration of platelets, and myelosuppression of platelet production due to HCV-induced bone marrow suppression. (Abd-El salam et al.,2016)

The response to eltrombopag is achieved via its interaction with the thrombopoietin receptor on megakaryocyte precursors and megakaryocytes in bone marrow to induce their proliferation and differentiation in order to increase platelet production. (Burness et al.,2014)

Conclusion:

Eltrombopag causes significant elevation of platelet count in patients with HCV related thrombocytopenia, so that Eltrombopag could be used prior to and during antiviral treatment when thrombocytopenia become confronting problem as well as before surgical interventions. Although more studies on larger number of patients are needed to validate the true indications, dosage schedule, therapeutic efficacy, and safety

profile of eltrombopag adjunct therapy in HCV-related thrombocytopenia.

References:

Abd-El salam S, Habba E, El Khalawany W (2016).

Correlation of platelets count with endoscopic findings in a cohort of Egyptian patients with liver cirrhosis. *Medicine*. 95(23):e3853.

Burness CB (2014). Eltrombopag: a review of its use in the treatment of thrombocytopenia in patients with chronic hepatitis C. *Drugs*. 74(16):1961–1971

Akahoshi T, Tomikawa M, Kawanaka H (2012). Laparoscopic splenectomy with interferon therapy in 100 hepatitis-C-virus-cirrhotic patients with hypersplenism and thrombocytopenia. *J Gastroenterol Hepatol*. 27(2):286–290.

Tchelepi H, Ralls PW, Radin R, Grant E (2002). Sonography of diffuse liver disease. *J Ultrasound Med*. 21(9):1023–1032.

Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R (1973). Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 60(8):646–649.

Afdhal NH, Dusheiko GM, Giannini EG (2014). Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infection and cirrhosis, allowing for effective antiviral therapy. *Gastroenterology*. 146(2):442–452.

Afdhal NH, Giannini EG, Tayyab G (2012). Eltrombopag before procedures in patients with cirrhosis

and thrombocytopenia. *N Engl J Med*. 367(8):716–724.

Peck-Radosavljevic M (2000). Thrombocytopenia in liver disease. *Can J Gastroenterol*. 14(Suppl D):60D–66D. *virus. Am J Med* 1994; 96: 124–32.

Cacoub P, Renou C, Rosenthal E (2000). Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'Etude et de Recherche en Medecine Interne et Maladies Infectieuses sur le Virus de l'Hepatitis C. *Medicine (Baltimore)*. 79(1):47–56.

Nurden AT, Viallard JF, Nurden P (2009). New-generation drugs that stimulate platelet production in chronic immune thrombocytopenic purpura. *Lancet*. 373(9674):1562–1569.

Tarantino MD, Bakshi KK, Brainsky A (2014). Hemostatic challenges in patients with chronic immune thrombocytopenia treated with eltrombopag. *Platelets* 25(1): 55