

## The Effect of Eltrombopag (Promecta) on Thrombocytopenia in Egyptian Patients with Chronic Hepatitis C

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### ABSTRACT

**AIM:** Chronic hepatitis C is the leading cause of chronic liver disease and cirrhosis in Egypt. Thrombocytopenia is one of its complications which may postpone or interfere with diagnostic and therapeutic procedures. One of the treatment options of thrombocytopenia is Eltrombopag, Eltrombopag is an orally bioavailability, low molecular weight non-peptide growth factor that is a selective c-Mpl agonist. We aimed to evaluate the ability of Eltrombopag to increase platelet counts in patients with HCV-related thrombocytopenia and to compare it with the use of haematinics.

**METHODS:** The study was conducted on 54 patients with HCV related chronic liver disease and thrombocytopenia (platelet count  $<75.000/\mu\text{L}$ ). All patients were subjected to complete history taking, clinical evaluation, laboratory investigations and abdominal ultrasonography. Patients were divided into three groups, group (I) twenty four patients received Eltrombopag, group (II) received vitamin B<sub>12</sub> and folic acid and group (III) who did not receive any haematinics and considered as a control group.

**RESULTS:** There was a significant rise in the platelet count in the Eltrombopag group after one and two weeks of treatment when compared to the other groups and more than half of the patients reached the target platelet count ( $>100,000/\mu\text{L}$ ) after two weeks of treatment with Eltrombopag. There was also a significant negative correlation between AST level and the dose of the drug and a significant positive correlation between the splenic size and the total grams of Eltrombopag needed to reach the target platelet count ( $p < 0.01$ ). So they may be used as predictors for the response to treatment. Other blood elements did not exhibit any changes during Eltrombopag treatment.

**CONCLUSIONS:** Eltrombopag causes significant selective elevation of platelet count in patients with HCV related thrombocytopenia; this can facilitate diagnostic and therapeutic interventions in such patients.

**Key words:** Chronic hepatitis C; Thrombocytopenia; Eltrombopag

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### INTRODUCTION

Thrombocytopenia is a common manifestation of chronic liver disease and it may exclude patients from interferon (IFN)-based antiviral therapy<sup>[1]</sup>.

The etiology of thrombocytopenia in chronic liver disease is multifactorial and HCV itself can cause megakaryocyte and platelet abnormalities by direct cytotoxicity or through indirect immunologic mechanisms<sup>[2]</sup>.

Studies showed that decreased production of platelets by megakaryocytes due to low thrombopoietin (TPO) concentration could be a possible cause of thrombocytopenia in liver cirrhosis and it was increased after orthotopic liver transplantation<sup>[3]</sup>.

Eltrombopag is a small-molecule of the biarylhydrazone class compounds of, non-peptide, oral platelet growth factor that acts as a thrombopoietin-receptor agonist<sup>[4]</sup>.

Eltrombopag is approved for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who has had an insufficient response to corticosteroids, immunoglobulins, or splenectomy<sup>[5]</sup>. So it can be used in patients with chronic liver diseases<sup>[6]</sup>.

So we aimed to evaluate the efficacy of Eltrombopag to increase the platelets count in patients with HCV-related thrombocytopenia and to compare it with the use of haematinics.

## METHODS

This study was conducted on 54 patients with HCV related chronic hepatitis and cirrhosis they were chosen from Kasr Al Aini outpatient clinic, Viral hepatitis center and the endemic medicine department faculty of medicine, Cairo University, El Menoufia national liver institute as well as from the internal medicine department, Faculty of Medicine, El Mansoura University, Egypt.

They were adult patients of both sexes with evidence of chronic HCV infection who must have a base line platelet count  $< 75,000/\mu\text{L}$ ; hemoglobin concentration  $\geq 11\text{g/dL}$  for men or  $\geq 10\text{g/dL}$  for women; absolute neutrophil count  $\geq 750/\text{mm}^3$  and no history of infections associated with neutropenia.

Patients with decompensated liver disease (Child Pugh score  $> 6$ ) or haemoglobinopathies were excluded from the study.

Patients with any prior history of arterial or venous thrombosis, hereditary thrombophilic disorders, hormone replacement therapy, systemic contraception (containing estrogen), smoking, diabetes, hypercholesterolemia, medication for hypertension or cancer, pre-existing cardiac disease or arrhythmias and any disease condition associated with active bleeding or requiring anticoagulation with heparin or warfarin all were excluded from the start.

Patients with any anti-neoplastic or immuno-modulatory treatment  $\leq 6$  months prior to the first dose of Eltrombopag or planning to have cataract surgery also were excluded.

Patients were subjected to detailed history taking, complete clinical examination as well as laboratory assessment including; (1) Complete liver and kidney functions; ALT, AST, ALP, serum albumin, creatinine and blood urea nitrogen; viral hepatitis markers (HCV Ab; HBs Ag and HBc Ab). Prothrombin time and concentration done to all patients and were (followed weekly for group I); (2) Complete blood count was done to all patients including haemoglobin level, RBCs count, total and differential leucocytic count and platelet count (repeated weekly for all patients till we reached the target platelets count); (3) Ocular examination: baseline fundus examination was done for all patients; (4) Pregnancy testing for female patients to exclude pregnancy; and (5) Labs to exclude the presence of other disease e.g. thyroid disease (Thyroid stimulating hormone, TSH), Auto-immune disease (Antinuclear antibody ANA) and diabetes (Random blood sugar RBS).

Abdominal ultrasounds as well as Doppler study were done to detect vessels patency, measure blood flow velocity and exclude any thrombosis in portal circulation before the use of Eltrombopag. Baseline echocardiography was also done. Approval from the institution ethical committee was obtained. A written informed consent was ob-

tained from each patient included in study regarding the study plane or the publication.

The patients were randomized into three groups with an informed consent.

**Group (I):** comprised 24 patients who received Eltrombopag.

**Group (II):** included 15 patients who were treated with haematinics (folic acid and vitamin B12).

**Group (III):** included 15 patients who did not receive any haematinics or any drugs affecting the platelet count serving as the control group.

The treatment endpoint was to reach platelet count of  $> 100,000/\mu\text{L}$  or to complete nine weeks of treatment.

### The patients treatment groups

**Group I:** Subjects initially received the lowest dose of Eltrombopag (25 mg once daily) for two weeks and if after this time the platelet count is  $< 100,000/\mu\text{L}$ , subjects underwent a sequential dose escalation to the next highest dose (50 mg once daily for up to two weeks), with further dose escalations to 75 mg once daily (up to two weeks) and 100 mg once daily (up to a maximum of three weeks) being available if platelet counts remain  $< 100,000/\mu\text{L}$ .

Patients were instructed not to take Eltrombopag within 2 hours of eating a meal or within 6 hours of taking any polyvalent cation containing antacids, calcium supplements, and/or vitamin supplements as the co-administration of polyvalent cations and Eltrombopag reduce the absorption of Eltrombopag by more than 50%. However, ingestion of water, black coffee or tea (i.e. without milk or cream) during this time is acceptable.

**Group II:** Subjects received fixed dose of folic acid 1000 mcg once daily and vitamin B12 400 mcg (bid) for nine weeks.

**Group III:** Subjects received liver supports without any haematinics.

**Statistical analysis:** patients' data were analyzed using SPSS 17.0 for windows 7. Quantitative variables were expressed by mean and SD (Standard deviation), compared using t-student and Mann-Whitney test, ANOVA test were used when appropriate.

Pearson correlation and Spearman's Roc were used for correlating quantitative variables, qualitative variables were expressed by numbers (Frequency) and percent compared between groups using Fisher's exact test and linear regression model were performed for calculating prediction models.

## RESULTS

The studied patients revealed no significant difference in the age ( $p = 0.2$ ), sex distribution ( $p = 0.311$ ), or residency ( $p = 0.632$ ) among the studied groups.

There was no significant difference in BMI, the clinical data, the Ultrasonographic findings as well as the laboratory parameters among the studied groups before treatment ( $p > 0.05$ ).

There was no significant difference in the haematological features of the studied groups ( $p > 0.05$ ) at the start of treatment as presented in table 1.

The platelet counts before the treatment, after one week, after two weeks of treatment were presented in table 2.

There was a significant positive correlation between the platelet count before treatment and the response after one week of treatment in group I ( $p < 0.001$ ).

Table 3 showed the mean difference in platelet count in different groups: On comparing the mean difference of platelet count between the Eltrombopag (group I) and the B<sub>12</sub> and folic acid (group II), the

mean difference (24,133.33) and it was significant ( $p < 0.001$ ).

The mean difference of platelet count between the Eltrombopag (group I) and the control group (group III) is (33800.00) and it was significant ( $p < 0.001$ ). The mean difference of platelet count between the B<sub>12</sub> and folic acid (group II) and the control group (group III) is (9666.66) and it was not significant ( $p = 0.156$ ).

There was a significant difference between the eltrombopag and B<sub>12</sub> and folic acid and between eltrombopag and control group while there was no significant difference between control group and B<sub>12</sub> and folic acid.

Table 4 showed the relation between the response after one week and other factors among the Eltrombopag patients. There was a significant positive correlation between the platelet count before treatment and the response after one week of treatment ( $p = 0.047$ ). There was a significant positive correlation between the AST level and the platelet count after one week of treatment ( $p = 0.013$ ). There was significant negative correlation between haemoglobin concentration and response after one week of treatment ( $p = 0.020$ ).

Table 5 documented the relation between the response after two weeks of treatment and other factors among the Eltrombopag patients. There was a significant positive correlation between the platelet count before treatment and the response after two weeks of treatment ( $p = 0.026$ ).

There was a significant positive correlation between the rise of platelet after one week of treatment and the response after two weeks ( $p = 0.000$ ). There was a significant positive correlation between the AST level and the platelet count after one week of treatment ( $p = 0.028$ ). There was significant negative correlation between haemoglobin concentration and response after one week of treatment ( $p = 0.005$ ).

There was a significant positive correlation between the platelet count before treatment and the platelet count at the end of treatment ( $p = 0.001$ ).

In order to establish a prediction model of the platelet count at the second week of treatment with Eltrombopag, we used multiple regression analysis and multiple correlation coefficients. The dependent variable was the platelet count at second week of treatment while the independent variables are: age, albumin level, gender, platelet count before treatment, AST, creatinine and WBC count. The only significant factor was the platelet count before treatment as ( $p < 0.004$ ) figure 1.

Table 6 and figure 2 demonstrated the number of patients reached the target platelet count (> 100,000) over the time in each group. All patients (100%) who received eltrombopag reached platelet count > 100,000/cmm, while only two patients (13.3%) received vitamin B<sub>12</sub> and folic acid reached the target platelet count and none of the patients in the control group reached the target platelet count.

Regarding the duration and the dose level of treatment needed to achieve the target platelet count in eltrombopag group, 26.7% after 1 week (25 mg daily), 26.7% after 2 weeks (25 mg daily), 20% after 3 weeks (shifted to 50 mg daily), 6.7% after 4 weeks (50 mg daily), 13.3% after 6weeks (75 mg daily) and 6.7% after 8 weeks (100 mg daily). While in group II, two patients reached the target platelet count (> 100,000/cmm) one after five weeks of treatment with vitamin B<sub>12</sub> and folic acid and the other patient after six weeks of treatment. There was no significant difference between platelet count before treatment and during the nine weeks among patients in the control group ( $p > 0.05$ ).

There was a significant difference between the Eltrombopag and B<sub>12</sub> and folic acid ( $p < 0.001$ ), and between Eltrombopag and control group ( $p < 0.001$ ); while there was no significant difference between

**Table 1** Hematological features in the studied groups before treatment.

	Group(I) (n=15) Mean ± SD	Group(II) (n=15) Mean ± SD	Group(III) (n=15) Mean ± SD
HB (g/dL)	13.87 ± 1.62	12.7 ± 1.64	12.95 ± 1.62
WBCS (× 10 <sup>3</sup> /µL)	4.91 ± 1.35	3.980 ± 1.02	4.307 ± 1.98
Platelets (× 10 <sup>3</sup> /µL)	54.2 ± 14.37	62.93 ± 17.95	59.6 ± 13.61

**Table 2** The platelet count before treatment, after one week and after two weeks of treatment in different groups.

	Group(I)	Group (II)	Group (III)
Platelet before treatment(×10 <sup>3</sup> /µL)	56.500 ± 3.709	62.933 ± 17.95	59.600 ± 13.610
After one week (×10 <sup>3</sup> /µL)	85.400 ± 41.918*	63.066 ± 14.542	59.000 ± 12.68
After two weeks (×10 <sup>3</sup> /µL)	133.733 ± 58.107**	61.866 ± 15.193	59.066 ± 11.45

\* $p < 0.05$ , \*\* $p < 0.001$ .

**Table 3** The mean difference in platelet count in different groups.

	Mean difference	Standard error	significance
Eltrombopag with B <sub>12</sub> and folic acid	24,133.33	4955.43	< 0.001*
Eltrombopag with control group	33800.00	4955.43	<0.001*
B <sub>12</sub> and folic acid with control group	9666.66	4955.43099	0.156

\* The mean difference is highly significant at  $p < 0.001$ .

**Table 4** The relation between the response after one week of treatment of Eltrombopag and other factors.

	Correlation coefficient (r)	Significance
Platelet count before treatment	0.520	0.047
AST level	0.623	0.013
Hb concentration	-0.591	0.020

**Table 5** The relations to the response after two weeks of treatment.

	Correlation coefficient (r)	Significance
Platelet count before treatment	0.572	0.026
Platelet count after one week of treatment	0.851	0.000
AST level	0.565	0.028
Hb concentration	-0.678	0.005

**Table 6** The number of patients reached the target platelet count (>100,000) in each group.

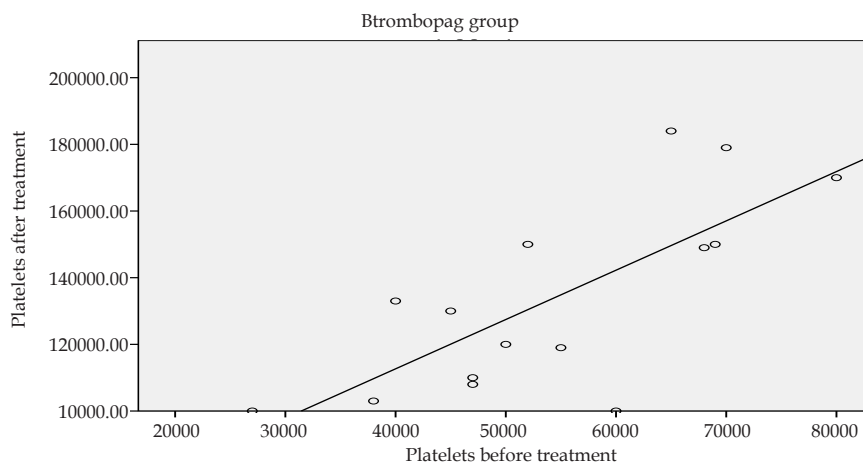
	Group (I)		Group (II)		Group (III)	
	No.	%	No.	%	No.	%
Week 1	7	29.17	0	0	0	0
Week 2	7	29.17	0	0	0	0
Week 3	4	16.67	0	0	0	0
Week 4	1	4.17	0	0	0	0
Week 5	0	0	1	6.7	0	0
Week 6	2	8.3	1	6.7	0	0
Week 7	0	0	0	0	0	0
Week 8	1	4.17	0	0	0	0
Week 9	2	8.3	0	0	0	0

control group and B<sub>12</sub> and folic acid ( $p > 0.05$ ).

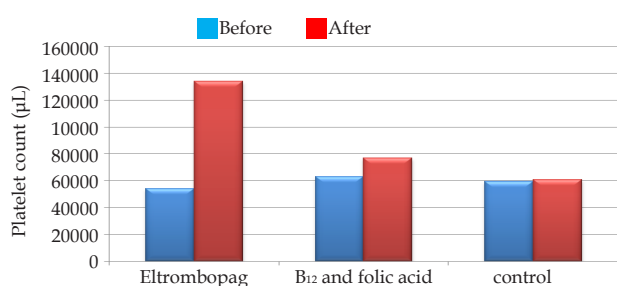
There were no severe or serious adverse events were occurred such as liver problems, bleeding or coagulopathy, bone marrow suppression or eye problems.

## DISCUSSION

Thrombocytopenia (platelet count <150,000/µL) is a common complication in patients with chronic liver disease (CLD)<sup>[7]</sup>. Eltrombopag is a small-molecule, non peptide, oral platelet growth factor that acts as a thrombopoietin-receptor agonist currently approved for the treatment of idiopathic thrombocytopenic purpura (ITP)<sup>[8]</sup> who has had an insufficient response to corticosteroids, immunoglobulins, or splenectomy<sup>[9]</sup>.



**Figure 1** The relation between the response at the end of treatment and platelet count before treatment.



**Figure 2** The platelet count before and after treatment.

In the present study we evaluated the impact of Eltrombopag in treatment of thrombocytopenia in patients with chronic HCV (GI = 24 patients), and comparing it with the administration of vitamin B<sub>12</sub> and folic acid (GII = 15 patients) and with no haematinics treatment in the control group (GIII = 15 patients). The patients received treatment for nine weeks or till the platelet count reached the target point (>100,000/µL).

In this study there was a significant rise in the platelet count in the Eltrombopag group after one and two weeks of treatment when compared to the other treatment groups. The patient received 25 mg daily and more than half of them reached the target platelet count (> 100,000/µL). This could be explained by phase I clinical study of Eltrombopag in which a consistent increase in platelet count started after 8 days of Eltrombopag use, and the time from first dose to peak was 16 days<sup>[10]</sup>.

The same findings were observed by Afdhal *et al*<sup>[11]</sup>, who studied the impact of Eltrombopag on thrombocytopenia due to HCV-related cirrhosis. During the initial treatment phase (four weeks), platelet counts were increased to 100,000/mL<sup>3</sup> or more in a dose-dependent manner among patients who received Eltrombopag but not in the placebo group. Also it has been observed by Bussel *et al*<sup>[8]</sup> and Danish *et al*<sup>[12]</sup>, that Eltrombopag increased platelet counts in a dose-dependent manner in patients with relapsed or refractory ITP.

To our knowledge there is no proved effect of haematinics use like B<sub>12</sub> and folic acid in the treatment of HCV related thrombocytopenia, despite it is a common practice to treat thrombocytopenia with haematinics, so our work didn't show any significant change in the platelet count in patients received B<sub>12</sub> and folic acid.

The manufacturer product information advised that in patients of East Asian descent or those with moderate or severe hepatic insufficiency the initial dose of Eltrombopag should be reduced to 25 mg once daily instead of the usual dose (50 mg/day)<sup>[13]</sup>. Despite that

all our patients had compensated liver (Child-Pugh A) they started with this low dose 25 mg/day and 53.4% of them reached the target platelet count with this dose.

In this study all the patients who received Eltrombopag reached the target platelet count within the nine weeks duration of treatment with starting dose 25 mg/day and raising the dose by 25 mg after two weeks if the target platelet count was not achieved, we found that 53.4% of the patients with the dose of 25 mg, 26.7% received 50 mg/day, 13.3% of patients received 75 mg/day and 6.7% received 100 mg/day reached the target platelet count.

Only two patients in the B<sub>12</sub> and folic acid group reached the target platelet count while none of the patients in the control group reached the target platelet count and this was similar to the results obtained by McHutchison *et al*<sup>[6]</sup>, who found that Eltrombopag improved the platelet count within four weeks of treatment while none of the patients received placebo reached the target platelet count.

In our study we found that there was a significant negative correlation between the AST level and the total grams of Eltrombopag needed to reach the target platelet count Esmat *et al* in 2007<sup>[14]</sup>, documented a strong correlation between the AST levels and the degree of fibrosis. This could be explained also by the higher plasma concentration and the longer the half life of Eltrombopag observed in patients with hepatic impairment<sup>[15]</sup>. Despite all our patients were Child-Pugh A; however the patients with more fibrosis and subsequently more hepatic impairment will have higher plasma level of Eltrombopag.

In our work we could find a positive significant correlation between the splenic size and the total grams of Eltrombopag needed to reach the target platelet count, and this went hand in hand with Akyüz *et al* study in 2007<sup>[16]</sup>, as they predicted a significant negative correlation between the platelet count and the splenic volume measured by magnetic resonant imaging.

To set a prediction model of the platelet count at the second week of treatment with Eltrombopag, we used multiple regression analysis and multiple correlation coefficients. The dependent variable was the platelet count at second week of treatment while the independent variables are: constant, age, albumin level, gender, platelet count before treatment, AST, creatinine and WBC count. The only significant factor was the platelet count before treatment and this went hand in hand with Hayes *et al*<sup>[17]</sup>, who found that the platelet count before treatment is predictor of response to Eltrombopag in patients with ITP.

There were no severe or serious adverse events were occurred such as liver problems, bleeding or coagulopathy, bone marrow suppression or eye problems and this was also documented by Wirea *et al*<sup>[18]</sup> so dose adjustment is not required.

## CONCLUSION

Eltrombopag (Promacta) causes significant elevation of platelet count in patients with HCV related thrombocytopenia, so that Eltrombopag could be used prior to and during treatment with Interferon and Ribavirin when thrombocytopenia become confronting problem as well as before surgical interventions.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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