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

Youssef Botros, Hanan Abdel Hafez, Rabab Fouad, Mayada El Negoly, Gamal Shiha, Imam Waked, Gamal EL Din Esmat

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 bioavailable, 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 /μL). 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 B12 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/μL) 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

© 2016 The Authors. Published by ACT Publishing Group Ltd.

Botros Y, Hafez HA, Fouad R, El Negoly M, Shiha G, Waked I, EL Din Esmat G. The Effect of Eltrombopag (Promecta) on Thrombocytopenia in Egyptian Patients with Chronic Hepatitis C. Journal of Gastroenterology and Hepatology Research 2016; 5(3): 2088-2092 Available from: URL: http://www.ghrnet.org/index.php/joghr/article/view/1703

INTRODUCTION

Thrombocytopenia is a common manifestation of chronic liver disease and it may exclude patients from interferon (IFN)-based antiviral therapy[1]. 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[2].
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[3].

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

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[5]. So it can be used in patients with chronic liver diseases[6].

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/μL; hemoglobin concentration ≥11g/dL for men or ≥10 g/dL for women; absolute neutrophil count ≥750/mm³ and no history of infections associated with neutropathy.

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

Patients with any anti-neoplastic or immuno-modulatory treatment or the publication.

**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 B12 and folate acid (group II), the
mean difference (24,133.33) and it was significant (p < 0.001).

The mean difference of platelet count between the Eitrombopag (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 B12 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 Eitrombopag and B12 and folic acid and between etrombopag and control group while there was no significant difference between control group and B12 and folic acid.

Table 4 showed the relation between the response after one week and other factors among the Eitrombopag 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 Eitrombopag 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 Eitrombopag, we used multiple regression analysis and multiple correlation coefficients. The dependent variable was the platelet count at second week of treatment and the response after two weeks of treatment (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 etrombopag reached platelet count > 100,000/cmm, while only two patients (13.3%) received vitamin B12 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 etrombopag 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 6 weeks (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 B12 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 Eitrombopag and B12 and folic acid (p < 0.001), and between Eitrombopag and control group (p < 0.001); while there was no significant difference between control group and B12 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)\[7\]. Eitrombopag 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)\[8\] who has had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.\[9\]
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 B₁₂ 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 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.

The same findings were observed by Afdhal et al[11], 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 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[9] and Danish et al[12], 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 B₁₂ 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 B₁₂ 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)[13]. 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 B₁₂ 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[8], 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[14], 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[15]. 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[16], 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[17], who found that the platelet count before treatment is predictor of response to Eltrombopag in patients with ITP.

---

**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.
There were no severe or serious adverse events were ocurred such as liver problems, bleeding or coagulopathy, bone marrow suppression or eye problems and this was also documented by Wirea et al[18] 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.

REFERENCES

1 Iga D, Tomimatsu M, Endo H, Ohkawa S, Yamada O. Improvement of thrombocytopenia with disappearance of HCV RNA in patients treated by interferon-alpha therapy: possible etiology of HCV-associated immune thrombocytopenia. Eur J Haematol 2005; 75: 417-423.
2 Weksler B.B. The pathophysiology of thrombocytopenia in hepatitis C virus infection and chronic liver disease. Aliment Pharmacol 2007; 26: 13-19.
3 Michiko O, Goshi S and Hironaka K. Thrombopoietin levels in serum and liver tissue in patients with chronic viral hepatitis and hepatocellular carcinoma. Clinical Science 2000; 99: 207-214.
4 Miller CL, DeLorme E, Tian SS, Hopson CB, Stark K, Giampa L, Valore EL, Dufty KJ, Luengo JL, Rosen J, Miller SG, Dillon SB, Lamb P. Discovery and characterization of a selective, non-peptidyl thrombopoietin receptor agonist. Exp Hematol 2005; 33(23): 85-93.
5 Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M, Arning M, Stone NL, Bussel JB. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase III study. Lancet 2011; 29(377): 393-402.
6 McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, Bouri鞠ere M, Berg T, Gordon SC, Campbell FM, Theodore D, Blackman N, Jenkins J, Afdhal NH. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. N Engl J Med 2007; 357(22): 2227-2236.
7 Tripodi A and Mannucci PM. Abnormalities of homeostasis in chronic liver disease: reappraisal of their clinical significance and need for clinical and laboratory research. J Hepatol 2007; 46: 727-733.
8 Bussel JB, Buchanan GR, Nugent DJ, Gnarra DJ, Bomgaars LR, Blanchette VS, Wang YM,Nie K, Jun S. A randomized, double-blind study of romiplostim to determine its safety and efficacy in children with immune thrombocytopenia. Blood 2011; 118(1): 28-36.
9 Tarantino MD, Bakshi KK, Brainsky A (2014): Hemostatic challenges in patients with chronic immune thrombocytopenia treated with eltrombopag. Platelets 2014, 25(1): 55-61.
10 Jenkins JM, Williams D, Deng Y, Uhl J, Kitchen V, Collins D, Erickson-Miller CL. Phase I clinical study of Eltrombopag, an oral, non-peptide thrombopoietin receptor agonist. Blood 2007; 109(11): 4739-4741.
11 Afkhal N, Dusheiko G, Giannini EG. Final Results of ENABLE 1, Phase III, Multicenter Study of Eltrombopag as an Adjunct for Anti-viral Treatment of Hepatitis C Virus-Related Chronic Liver Disease Associated With Thrombocytopenia. 62nd AASLD 2011; San Francisco, CA; Abst. LB-3.
12 Danish FA, Koul SS, Subhani FR, Rabbani AE, Yasmin S. Considerations in the management of hepatitis C virus-related thrombocytopenia with Eltrombopag. Saudi J Gastroenterol 2010; 16(1): 51-56.
13 GlaxoSmithKline. Promacta® (eltrombopag) Tablets Product Information, Research Triangle Park, NC. October 2008.
14 Esmat G, Metwally M, Zalata KR, Gadalla S, Abdel-Hamid M, Abouzied A, Shaheen AA, El-Raziky M, Khabat H, El-Kaffrawy S, Mikhail N, Magder LS, Afkhal NH, Strickland GT. Evaluation of serum biomarkers of fibrosis and injury in Egyptian patients with chronic hepatitis C. J Hepatol 2007; 46(4): 620-627.
15 Bauman JW, Vincent CT, Peng B, Wire MB, Williams DD, Park JW. Effect of hepatic or renal impairment on eltrombopag pharmacokinetics. J Clin Pharmacol 2011; 51(5): 739-750.
16 Akyüze F, Yokeler E, Kaymakoğlu Ş, Horasanli S, İbrişim D, Demir K, Aksoy N, Poturoğlu S, Badur S, Ökten A. The role of thrombopoietin and spleen volume in thrombocytopenia of patients with non-cirrhotic and cirrhotic portal hypertension. Turk J Gastroenterol 2007; 18(2): 95-99.
17 Hayes S, Ouellet D, Zhang J, Wire MB, Gibiansky E. Population PK/PD modeling of Eltrombopag in healthy volunteers and patients with immune thrombocytopenic purpura and optimization of response-guided dosing. J Clin Pharmacol 2011; 51(10): 1403-1417.
18 Wire MB, Fang L, Hussaini A, Kleha JF, Theodore D. Lack of clinically significant pharmacokinetic interaction between the thrombopoietin receptor agonist eltrombopag and hepatitis C virus protease inhibitors boceprevir and telaprevir. Antimicrobial agents and chemotherapy Antimicrobial Agents Chemotherapy 2014; 58 (11): 6704-9.

Peer reviewer: Ming-Hua Zheng, MD, Associate Professor, 1Department of Infection and Liver Diseases, Liver Research Center, The First Affiliated Hospital of Wenzhou Medical College, No.2 Fuxue lane, Wenzhou, 325000, China.