Eltrombopag in chronic hepatitis C

Romeo-Gabriel Mihăilă, Remus-Călin Cipăian

Romeo-Gabriel Mihăilă, Remus-Călin Cipăian, Faculty of Medicine, “Lucian Blaga” University of Sibiu, Sibiu, Cod 550169, Romania

Author contributions: Mihăilă RG and Cipăian RC contributed solely and equally to this work.

Correspondence to: Romeo-Gabriel Mihăilă, MD, PhD, Associate Professor, Faculty of Medicine, “Lucian Blaga” University of Sibiu, str Lucian Blaga, Nr 2A, Sibiu, Cod 550169, Romania. romeomihaila@yahoo.com

Telephone: +40-269-215050 Fax: +40-269-218365

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Abstract

Chronic hepatitis C is a public health problem worldwide. Unfortunately, not all patients may benefit from antiviral therapy due to thrombocytopenia. Its causes are represented by portal hypertension and platelet sequestration in the spleen, decreased serum levels or activity of thrombopoietin, the bone marrow suppression induced by hepatitis C virus and a possible adverse effect of interferon. Thrombopoietin receptor analogs may contribute to increased platelet counts in these patients. Eltrombopag binds to another region of the thrombopoietin receptor compared to endogenous thrombopoietin and stimulates the proliferation and maturation of megakaryocytes and the platelet production in a dose-dependent manner. Eltrombopag has proven its effectiveness for the treatment of patients with primary immune thrombocytopenia. It indications for other hemopathies or situations (like thrombocytopenia secondary to chemoradiotherapy, acute leukemia, myelodysplastic syndroms, acquired and hereditary bone marrow failure, and platelet donors) is under study. Eltrombopag may be particularly useful in patients with advanced chronic hepatitis or liver cirrhosis who require antiviral treatment. We present a minireview on the results of treatment with eltrombopag in patients chronically infected with hepatitis C, highlighting the benefits and mentioning possible adverse effects. In some studies eltrombopag increased the number of virological responses after classical antiviral treatment of patients with chronic hepatitis C and reduced the transfusional requirements of those who had to be subjected to invasive surgery. Eltrombopag is a solution for many of these patients, which allows them receiving antiviral therapy and sometimes getting a sustained virological response, but they must be well monitored to prevent possible thromboembolic or bone marrow complications or liver failure occurrence.

Key words: Eltrombopag; Chronic hepatitis C; Hepatitis C virus; Platelets; Thrombocytopenia

Core tip: Chronic hepatitis C is a public health problem worldwide. Unfortunately, not all patients may benefit from antiviral therapy due to thrombocytopenia. Thrombopoietin receptor analogs may contribute to increased platelet counts in these patients. We present a minireview on the results of treatment with eltrombopag in patients chronically infected with hepatitis C, highlighting the benefits and mentioning possible adverse effects. Eltrombopag is a solution for many of these patients, which allows them receiving antiviral therapy and sometimes getting a sustained virological response, but they must be well monitored to prevent possible thromboembolic or bone marrow complications or liver failure occurrence.

INTRODUCTION

To obtain sustained virological response it is recommended that patients with chronic hepatitis C are treated with at least 80% of the required dose for at least 80% of the length required. This requires adherence of patients...
and avoid dangerous cytopenias. The introduction of erythropoietic agents for the control of hemolytic anemia induced by ribavirin and granulocyte colony stimulating factor to combat neutropenia produced by pegylated interferon allowed to maintain the classic treatment of chronic liver diseases induced by hepatitis C virus in a larger number of patients, although the effect on sustained virological response is controversial. Just in an article that refers to the administration of darbepoetin and filgrastim was found an improvement of sustained virological response.

The thrombocytopenic patients with chronic hepatitis C cannot benefit from therapy with pegylated interferon and ribavirin, fact which allows the continuation of virus replication, as well as the aggravation and the progression of chronic hepatopathy. Furthermore, interferon therapy can worsen thrombocytopenia, risking to reduce dosage or stopping the antiviral treatment. It is believed that about 13% of patients with liver cirrhosis have a number of platelets between 5000/mm$^3$ and 75000/mm$^3$ (moderate thrombocytopenia). Its causes are represented by portal hypertension and platelet sequestration in the spleen, decreased serum levels or activity of thrombopoietin, the bone marrow suppression induced by hepatitis C virus and a possible adverse effect of interferon.

Thrombopoietin is produced in the liver and is involved in the proliferation and differentiation of megakaryocytes and in increasing platelets release from them. Stimulation of platelet production may be a solution to reduce the level of thrombocytopenia and for initiating or continuing antiviral therapy in chronic liver disease caused by hepatitis C virus. We present a mini-review on the results of treatment with eltrombopag, a thrombopoietin receptor analog, administered to patients chronically infected with hepatitis C virus. We have analyzed all 44 PubMed articles containing the keywords eltrombopag and chronic hepatitis C, presented on 31 December 2013.

**STIMULATING THE PRODUCTION OF PLATELETS**

The activation of platelets production in the megakaryocytes is done by stimulating the thrombopoietin receptor, followed by activation of JAK-STAT mechanism. The thrombopoietin receptor can be activated by endogenous thrombopoietin (produced in the liver), recombinant human thrombopoietin molecules (which have the disadvantage that consists in the possibility of development of antibodies against them), that may cross react with endogenous thrombopoietin which is why the clinical trials with them were stopped in 2001 and thrombopoietin receptor analogs (second-generation thrombopoietin receptor agonists), more recently introduced into clinical practice, that have no homology to human thrombopoietin. This second generation of promoters of platelets production is represented by eltrombopag (the first thrombopoietin receptor analogue), romiplostim (AMG 511) - a peptidic agonist, and Peg-TPOmp, and small antibodies that were engineered.

Unlike romiplostim, which is administered parenterally, the treatment with eltrombopag (a small-molecule, non-peptide, thrombopoietin mimetic) is done orally. Emtrombopag binds to another region of the thrombopoietin receptor compared to endogenous thrombopoietin, that does not enter in competition with them. It stimulates the proliferation and maturation of megakaryocytes and the platelet production in a dose-dependent manner. Even after their administration at healthy subjects the effect begins just after 5 d and reaches a maximum at 12-14 d of treatment. Their efficacy was proven in ITP and thrombocytopenia from chronic hepatitis C.

Romiplostim is given parenterally in a dose of 2 µg/kg per week, with subsequent possibility of increasing it at intervals of 2 wk, with the same precautions as in the case of eltrombopag. It has also proved to be effective in some cases of chronic hepatitis C treated with antiviral medication and as preoperative therapy. But, it must be administered parenterally and weekly. If the platelet count increases over the desired value, the effect will persist longer than in the case of eltrombopag, which is also easier to give (orally).

Eltrombopag may be particularly useful in patients with advanced chronic hepatitis or liver cirrhosis who require antiviral treatment. If the number of platelets is less than 25000/mm$^3$ it is recommended to give 25 mg of eltrombopag daily, in order to attain the target value that allows to start the administration of pegylated interferon and ribavirin. Blood count control will be made weekly before initiating antiviral therapy and subsequently until the stabilisation of their number and monthly thereafter. The dose can be increased with 25 mg (every 2 wk) so platelets should be between 50000-100000/mm$^3$. If their number exceeds 100000/mm$^3$ the dose will be decreased with 25 mg every 2 wk, and if they exceed 150000/mm$^3$ the therapy will be stopped, and it will be resumed once their numbers will drop below 100000/mm$^3$, but with a dose of 25 mg less, with a check of blood cell count 2 times per week. If the patient has liver failure, he must wait 3 wk before increasing the dose. Assessing their usefulness in thrombocytopenia secondary to chemo- or radiotherapy, in acute leukemia, myelodysplastic syndroms, acquired and hereditary bone marrow failure, and platelet donors is under study. Emtrombopag is good tolerated but it should not be given together with polyclonal cations, including calcium that can be bind to the drug in the digestive tract. The most common significant potential side effects of eltrombopag are nausea, vomiting, headache, dry mouth, and abdominal pain, and the most serious - the appearance of thromboembolic events, decompensation of liver disease, increasing bone marrow blasts, and reticulin bone marrow fibrosis. Before starting eltrombopag treatment it is recommended to make a peripheral blood smear to study the morphology of figurative elements. After the establishment of a fixed
dose of medication, it is advisable to make a blood count and a peripheral blood smear monthly throughout the duration of the treatment, to refer the matter to the occurrence of morphological abnormalities, cytopenia, immature cells, or with dysplasia, in which case the drug will be stopped and a bone marrow aspiration and biopsy will be made; the slides will be colored for bone marrow cell study and for the possible fibrosis (sections of biopsy) emphasizing. The treatment must be carefully monitoring. There are criteria for eltrombopag discontinuation in patients with liver cytolysis or clinical signs of liver disease worsening. If the patient has baseline serum albumins under 35 g/L or MELD score ≥ 19, the risk-benefit ratio before starting treatment with eltrombopag will be examined carefully, and in the case of its beginning the patient will be surveyed on the occurrence of clinical symptoms and signs pleading for hepatic decompensation and hepatic function will be monitored closely by the hepatologist (at least monthly). On a monthly basis and in the event of clinical manifestations suggestive for an abdominal vein thrombosis (especially of the portal vein) a Doppler ultrasound examination of the abdomen is recommended for its confirmation, in which case eltrombopag must be stopped and an anticoagulation therapy will be initiate, unless there are contra-indications. Thrombocytopenia may be due to human immunodeficiency virus infection. The association of HIV-protease inhibitors lopinavir + ritonavir in dose of 400/100 mg BID with eltrombopag in dose of 100 mg can reduce the area under the plasma concentration-time curve of the last by about 17%.

CLINICAL TRIALS

Thrombopoietin-receptor agonists proved to be extremely useful for the thrombocytopenic patients chronically infected with hepatitis C virus: the increase of platelets number allows initiation and continuation of classic antiviral therapy, with the chance to obtain sustained virological response at many of them. The increase of the number of platelets allows sometimes to perform the liver biopsy or other invasive proceedings (including surgery). Eltrombopag increases the number of platelets in a dose-response manner. In many clinical trials it achieved the goal of platelets number (≥ 50000/mm<sup>3</sup>). Even a Cochrane review that included articles published between January 1966 - March 2010 established that eltrombopag was superior to palcebo on increasing the number of platelets. One of the cytied studies mentioned this last period, the number of platelets decreased (effect probably due to the pegylated interferon), but it remained considerably above baseline levels.

A review of clinical and preclinical studies of eltrombopag for the treatment of patients with chronic liver diseases made prior to October 2012 has established that this analogue of thrombopoietin receptor increased the number of sustained virological responses after classical antiviral treatment of those with chronic hepatitis C and reduced the transfusional requirements of those who had to be subjected to invasive surgery.

The phase 3 randomized, controlled trials ENABLE-1 and ENABLE-2 studied the efficacy of eltrombopag given to patients with chronic hepatitis C and thrombocytopenia (under 75000/mm<sup>3</sup>) for ≤ 9 wk concerning the initiation and the maintaining antiviral therapy. A number of platelets ≥ 50000/mm<sup>3</sup> was obtained more frequently in patients treated with eltrombopag, a fact that has allowed them to be treated with higher doses of pegylated interferon. Sustained virological response was more frequent in patients treated with eltrombopag in dose of 25-100 mg daily compared to placebo. Hepatic decompensation occurred in a higher percentage in those treated with eltrombopag than in the placebo group (10% vs 5%). Thromboembolic complications were observed more frequently in the group treated with eltrombopag of ENABLE-2 study. In a study of phase 2, the treatment of the patients with chronic hepatitis C with peginterferon and ribavirin could be initiated and continued for 12 wk at 36% of those who received eltrombopag 30 mg/d, at 53% of those treated with eltrombopag 50 mg/d, at 65% of those who received eltrombopag 75 mg daily, and at only 6% in those who received placebo.

At week 2 of treatment with eltrombopag given for trombocytopenia in a randomized, open-label, phase II study, the patients with chronic hepatitis C obtained a mean elevation of trombocytes of 24800/mm<sup>3</sup> after 12.5 mg/d, 54000/mm<sup>3</sup> after 25 mg/d, and 60000/mm<sup>3</sup> after 37.5 mg/d, a fact that demonstrated its effectiveness.

The patients with liver cirrhosis produced by hepatitis C virus have frequently trombocytopenia. In a clinical trial, 74 of such patients with a number of platelets between 20000/mm<sup>3</sup> and 70000/mm<sup>3</sup> were randomized to be treated with eltrombopag or placebo. A proportion of 75%, 79%, and respectively 95% of patients treated with 30 mg/d, 50 mg/d, and respectively 75 mg/d obtained a number of platelets over 10000/mm<sup>3</sup> at week 4. No patient in the placebo group had such a platelet growth. This has allowed the initiation of therapy with pegylated interferon and ribavirin and, to a significant proportion of patients, completing the proposed therapy for 12 wk. In this last period, the number of platelets decreased (effect probably due to the pegylated interferon), but it remained considerably above baseline levels.

Immune thrombocytopenic purpura (ITP) can also occur in the patients with chronic liver diseases due to hepatitis C virus infection. This combination of disorders seems to raise particular problems due to possible treatment complications. Such a case of a 78-year-old woman with cirrhosis, ITP and epistaxis was recently published. Due to the fact that prednisolone (0.5 mg/kg per day) was inefficient, she received eltrombopag (12.5 mg/d) under which the number of platelets increased, but after fifty-four days of treatment a portal vein thrombosis appeared. After eltrombopag stopping, under antithrombin III treatment she developed deep vein and pulmonary artery thromboses. Long-term treatment with heparin and then with warfarin was effective. Thrombocytopenic
patients with chronic liver diseases are more prone to develop thrombotic complications under eltrombopag treatment, even at lower doses than those used in ITP. The thrombotic risk is especially important in patients with chronic liver diseases which have to be subjected to invasive procedures, if the number of platelets increases by over 200000/mm³. Even in hemophilic patients with chronic liver disease it is recommended that treatment with eltrombopag has to begin with a slow dose (25 mg/d) and to be subsequently amended so that the number of platelets to be maintained between 50000-100000/mm³, due to the fact that they also have thrombotic risk under eltrombopag [25].

An elderly patient included in a chronic hemodialysis program for its chronic kidney disease was treated for severe thrombocytopenia with platelet transfusions and multiple drugs, including eltrombopag, for 6 wk, but without therapeutic answer. Romiplostim allowed to normalize the number of platelets in a dose of 5 μg/kg weekly, then reduced to half [26]. There are opposite cases, too: patients did not respond to romiplostim, but they responded to eltrombopag, so that in case of an inadequate response to one of the thrombopoietin receptor agonists it is recommended to be tested the treatment with the other one.

In turn, antiviral treatment of chronic hepatitis C contributes effectively to the reduction or disappearance of thrombocytopenia sometimes associated with this infection [27].

CONCLUSION
Administration of eltrombopag in thrombocytopenic patients chronically infected with hepatitis C virus contributes to the reduction of the number of patients infected with this virus by the opportunity to receive antiviral treatment and obtain sustained virological response. Even if this goal is not achieved, pegylated interferon therapy reduces the rate of progression of liver fibrosis. E1trombopag therapy should be closely monitored in these patients, who are prone to develop thrombotic or bone marrow complications, or liver failure. E1trombopag is a revolutionary solution for those patients who require to medical world also a deepening understanding of the interrelations between coagulation and chronic liver diseases. To what extent liver fibrogenesis can be activated by coagulation activation? Fundamental research and clinical practice will have to respond in time to this problem.

REFERENCES
1 Tyagi P, Madan K. Have hematopoietic growth factors made an impact on the management of liver disease? Trop Gastroenterol 2008; 29: 187-193 [PMID: 1932086]
2 Tillmann HL, McHutchison JG. Use of thrombopoietic agents for the thrombocytopenia of liver disease. Semin Hematol 2010; 47: 266-273 [PMID: 20620438 DOI: 10.1053/j.semihematol.2010.04.003]
3 McCormick PA, Murphy KM. Splenomegaly, hypersplenism and coagulation abnormalities in liver disease. Baillieres Best Pract Res Clin Gastroenterol 2000; 14: 1009-1031 [PMID: 11139352 DOI: 10.1053/bega.2000.0144]
4 Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, Weksler B, Esteban R. Thrombocytopenia associated with chronic liver disease. J Hepatol 2008; 48: 1000-1007 [PMID: 18433919 DOI: 10.1016/j.jhep.2008.03.009]
5 Wörrmann B. Clinical indications for thrombopoietin and thrombopoietin-receptor agonists. Transfus Med Hemother 2013; 40: 319-325 [PMID: 24273485 DOI: 10.1159/000355006]
6 Kuter DJ. The biology of thrombopoietin and thrombopoietin receptor agonists. Int J Hematol 2013; 98: 10-23 [PMID: 23821332 DOI: 10.1007/s12185-013-1382-0]
7 Homeida S, Eldon C, Betty P, Jackson B, Kolade S, Bateman C, Peng YY, Stasi R. New thrombopoietin receptor agonists for platelet disorders. Drugs Today (Barc) 2012; 48: 293-301 [PMID: 22536571 DOI: 10.1358/dott.2012.48.1.1740505]
8 Bussel JB, Pinheiro MP. E1trombopag. Cancer Treat Rev 2011; 37: 289-303 [PMID: 21052963 DOI: 10.1016/j.ctvr.2010.12.004]
9 Afdhal NH, McHutchison JG. Review article: pharmacological approaches for the treatment of thrombocytopenia in patients with chronic liver disease and hepatitis C infection. Aliment Pharmacol Ther 2007; 26 Suppl 1: 29-39 [PMID: 17958517 DOI: 10.1111/j.1365-2036.2007.03511.x]
10 Kuter DJ. Romiplostim. Cancer Treat Rev 2011; 37: 267-288 [PMID: 21052962 DOI: 10.1016/j.ctvr.2010.12.004]
11 Kuter DJ. New thrombopoietic growth factors. Curr Lymphoma Myeloma 2009; 9 Suppl 3: S347-S356 [PMID: 19778863 DOI: 10.3816/CLM.2009.s.034]
12 McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, Bourliere M, Berg T, Gordon SC, Campbell FM, Theodore D, Blackman N, Jenkins J, Afdhal NH. E1trombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. N Engl J Med 2007; 357: 2227-2236 [PMID: 18046027 DOI: 10.1056/NEJMoa073255]
13 Jenkins JM, Williams D, Deng Y, Uhl J, Kitchen V, Collins D, Erickson-Miller CL. Phase 1 clinical study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist. Blood 2007; 109: 4739-4741 [PMID: 17327409 DOI: 10.1182/blood-2007-03-079485]
14 Zhang Y, Kolesar JM. E1trombopag: an oral thrombopoietin receptor agonist for the treatment of idiopathic thrombocytopenic purpura. Clin Ther 2011; 33: 1560-1576 [PMID: 22054810 DOI: 10.1016/j.clinthera.2011.10.004]
15 Giannini EG, Afdhal NH. E1trombopag in patients with chronic liver disease. Expert Opin Pharmacother 2012; 13: 669-678 [PMID: 23452139 DOI: 10.1517/14656566.2012.737529]
16 Corman SL, Mohammad RA. E1trombopag: a novel oral thrombopoietin receptor agonist. Am J Hematol 2010; 85: 1072-1079 [PMID: 20460556 DOI: 10.1345/aph.1P342]
17 Wire MB, McLean HB, Pendry C, Theodore D, Park JW, Peng B. Assessment of the pharmacokinetic interaction between eltrombopag and lopinavir-ritonavir in healthy adult subjects. Antimicrob Agents Chemother 2012; 56: 2846-2851 [PMID: 22931553 DOI: 10.1128/AAC.05214-11]
18 Casciano PA, Bussel JB. Thrombopoietin-receptor agonists. Curr Opin Hematol 2012; 19: 392-398 [PMID: 22872157 DOI: 10.1097/MOH.0b013e32835e6909]
19 Mac Nicholas R, Norris S. Review article: optimizing SVR and management of the haematological side effects of peginterferon/ribavirin antiviral therapy for HCV - the role of epoetin, G-CSF and novel agents. Aliment Pharmacol Ther 2010; 31: 929-937 [PMID: 20757617 DOI: 10.1111/j.1365-2036.2010.04269.x]
20 Danish FA, Koul SS, Subhani FR, Rabbanii AE, Yasmin S. Considerations in the management of hepatitis C virus-related thrombocytopenia with eltrombopag. Saudi J Gastroenterol 2010; 16: 51-56 [PMID: 20655789 DOI: 10.1016/j.sjg.2010.06.002]
21 Afdhal NH, Dusheiko GM, Giannini EG, Chen PJ, Han KH, Mohsin A, Rodriguez-Torres M, Rugina S, Bakulin I, Lawtze E, Shiffman ML, Tayyab GU, Poordad F, Kamel YM, Brainsky
A, Geib J, Vassey SY, Patwardhan R, Campbell FM, Theodore D. Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infection and cirrhosis, allowing for effective antiviral therapy. Gastroenterology 2014; 146: 442-452. e1 [PMID: 24126979 DOI: 10.1053/j.gastro.2013.10.012]

22 Tillmann HL, Patel K, McHutchison JG. Role of growth factors and thrombopoietic agents in the treatment of chronic hepatitis C. Curr Gastroenterol Rep 2009; 11: 5-14 [PMID: 19166653]

23 Kawaguchi T, Komori A, Seike M, Fujiyama S, Watanabe H, Tanaka M, Sakisaka S, Nakamuta M, Sasaki Y, Oketani M, Hattori T, Katsura K, Sata M. Efficacy and safety of eltrombopag in Japanese patients with chronic liver disease and thrombocytopenia: a randomized, open-label, phase II study. J Gastroenterol 2012; 47: 1342-1351. [PMID: 22674141 DOI: 10.1007/s00535-012-0600-5]

24 Kawano N, Hasuike S, Iwakiri H, Nakamura K, Ozono Y, Kusumoto H, Nagata K, Kikuchi I, Yoshida S, Kuriyama T, Yamashita K, Muranaka T, Kawaguchi T, Sata M, Okamura T, Ueda A, Shimoda K. Portal vein thrombosis during eltrombopag treatment for immune thrombocytopenic purpura in a patient with liver cirrhosis due to hepatitis C viral infection. J Clin Exp Hepatol 2013; 3: 151-155 [PMID: 23995112]

25 Aguilar C. Potential usefulness of thrombopoietin receptor agonists in haemophiliacs with thrombocytopenia due to chronic liver disease. Blood Coagul Fibrinolysis 2013; 24: 231-236 [PMID: 23518832 DOI: 10.1097/MBC.0b013e3283606a0b]

26 Al-Jafar H, Giagounidis A, El-Rashaid K, Al-Ali M, Hakim AA. Use of romiplostim in a hemodialysis patient with primary immune thrombocytopenia. Ann Pharmacother 2012; 46: e31 [PMID: 23115229 DOI: 10.1345/aph.1R134]

27 Stasi R, Chia LW, Kalkur P, Lowe R, Shannon MS. Pathobiology and treatment of hepatitis virus-related thrombocytopenia. Mediterr J Hematol Infect Dis 2009; 1: e2009023 [PMID: 21415958 DOI: 10.4084/MJHID.2009.023]

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