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Eltrombopag in chronic hepatitis C

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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 increase 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. Its indication for other hemopathies or situations (like thrombocytopenia secondary to chemo- or radiotherapy, 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 virus, highlighting the benefits and mentioning possible adverse effects. In some studies eltrombopag increased the number of virological responses after clasical 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.

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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[1].

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[2], 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 50000/mm^3 and 75000/mm^3 (moderate thrombocytopenia). Its causes are represented by portal hypertension[3] 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[4].

Thrombopoietin is produced in the liver and is involved in the proliferation and differentiation of megakaryocytes and in increasing platelets release from them[5].

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[6], that may cross react with endogenous thrombopoietin[7] which is why the clinical trials with them were stopped in 2001[5]) and thrombopoietin receptor analogs (second-generation thrombopoietin receptor agonists), more recently introduced into clinical practice[6], that have no homology to human thrombopoietin[7]. This second generation of promoters of platelets production is represented by eltrombopag (the first thrombopoietin receptor analogue[8]), romiplostim (AMG 531) - a peptidic agonist, and Peg-TPOmp, and small antibodies that were engineered[9].

Unlike romiplostim, which is administered parenteraly, the treatment with eltrombopag (a small-molecule, non-peptide, thrombopoietin mimetic[10]) is done orally. Eltrombopag binds to another region of the thrombopoietin receptor compared to endogenous thrombopoietin, that does not enter in competition with them tying[11]. It stimulates the proliferation and maturation of megakaryocytes and the platelet production in a dose-dependent manner[12,13]. Even after their administration at healthly 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 parenteraly 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[1]. 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 allowes to start the administration of pegylated interferon + 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 stoped, 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[14], acquired and hereditary bone marrow failure[5], and platelet donors is under study[6]. Eltrombopag is good tolerated[2] but it should not be given together with polyvalent cations, including calcium[8] that can bind to the drug in the digestive tract. The most common significant potential side effects of eltrombopag are nausea, vomiting[14], headache, dry mouth, and abdominal pain[12], and the most serious - the appearance of thromboembolic events, decompensation of liver disease[15], increasing bone marrow blasts[11], and reticulin bone marrow fibrosis[11,14]. 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[16]. If the patient has baseline serum albumins under 35 g/L or MELD score $\geqslant$ 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%[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[18,19], with the chance to obtain sustained virological response at many of them. The increase of the number of platelets allows sometimes to performe the liver biopsy or other invasive proceedings (including surgery)[4]. Eltrombopag increases the number of platelets in a dose-response manner[2]. In many clinical trials it achieved the goal of platelets number ($\geqslant$ 50000/mm^3)[20]. 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 cyted studies mentioned its efficacy on the treatment of thrombocytopenia in patients with cirrhosis due to hepatitis C virus infection[16].

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 clasical antiviral treatment of those with chronic hepatitis C and reduced the transfusional requirements of those who had to be subjected to invasive surgery[15].

The phase 3 randomized, controlled trials ENABLE-1 and ENABLE-2 studied the efficacity of eltrombopag given to patients with chronic hepatitis C and thrombocytopenia (under 75000/mm^3) for $\leqslant$ 9 wk concerning the initiation and the maintaining antiviral therapy. A number of platelets $\geqslant$ 50000/mm^3 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[21]. 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[22].

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^3 after 12.5 mg/d, 54000/mm^3 after 25 mg/d, and 60000/mm^3 after 37.5 mg/d[23], 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^3 and 70000/mm^3 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 100000/mm^3 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[12].

Immune thrombocytopenic purpura (ITP) can also occure 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[24]. 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/mm^3. Even in hemophiliac 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/mm^3, 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 trombopoietin receptor analogues it is recommanded 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. Eltrombopag therapy should be closely monitored in these patients, who are prone to develop thrombotic or bone marrow complications, or liver failure. Eltrombopag is a revolutionary solution for those patients who require to medical world also a deepen 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.

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