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MINIREVIEWS

Use of eltrombopag in thrombocytopenia of liver disease

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Abstract

Second generation thrombopoietin agonists including eltrombopag and romiplostim act on the thrombopoietin receptor to increase the megakaryocyte production. These agents were needed as use of first generation recombinant products was associated with formation of autoantibodies. Eltrombopag is an oral thrombopoietin agonist found effective in raising platelet counts in patients with immune thrombocytopenia. The drug has now been found to be useful in raising platelet counts in thrombocytopenia related to liver disease including cirrhosis and chronic viral hepatitis. Although the drug may help enable adequate interferon therapy in patients with HCV infection and help carry out invasive procedures in patients with cirrhosis, concerns have been raised of possible thrombotic complications including portal vein thrombosis. Randomized trials have shown that use of eltrombopag concomitant with pegylated interferon and ribavirin increased the chances of sustained virologic response while decreasing the dose reductions of interferon. The data on use of romiplostim in these clinical indications is also emerging. However, in the future, availability of interferon free regimens is likely to decrease the use of eltrombopag for enabling antiviral therapy. The review discusses the role of eltrombopag in management of liver disease related thrombocytopenia in wake of recent data as also the dosage, precautions and adverse effects associated with its use.

Key words: Cirrhosis; Thrombopoietin; Eltrombopag; Romiplostim; Hepatitis; Hepatitis C virus; Splenectomy; Thrombocytopenia

Core tip: Thrombocytopenia associated with liver disease is multifactorial. Eltrombopag, a thrombopoietin agonist, has been found useful in increasing platelet counts in these patients. It has been clinically used to increase platelet counts in cirrhotic patients prior to invasive procedures and in patients with chronic hepatitis C to enable administration of interferon based antiviral therapy. However, there are concerns regarding its safety and possible increased risk of portal vein thrombosis.

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INTRODUCTION

The recent advances in management of immune thrombocytopenia seem to have rubbed off on the management of thrombocytopenia in liver disease. The availability of thrombopoietin agonists in recent times has added to the armamentarium to manage liver disease related thrombocytopenia. The present review focuses on the evidence regarding clinical use of eltrombopag (marketed as Revolade and Promacta) in liver disease related thrombocytopenia.

THROMBOCYTOPENIA IN LIVER DISEASE

Thrombocytopenia is an important complication of chronic liver disease but may accompany non-cirrhotic liver disease. Although various authors have used different definitions, any level of platelets below 150000/mm^3

Table 1 Mechanisms of thrombocytopenia in liver disease

In chronic liver disease
Decreased Thrombopoietin production
Splenic sequestration
Autoantibodies against platelets
Expansion of plasma volume
Bone marrow suppression (Alcohol)
In specific liver diseases
Viral or alcohol related marrow suppression
Autoimmune thrombocytopenia
Cryoglobulins
Drugs: Interferon mediated marrow suppression

would qualify as thrombocytopenia[1]. The incidence of thrombocytopenia has been reported from 15% to 75%[2,3]. Multiple mechanisms may contribute to the genesis of thrombocytopenia in association with liver disease[2,4]. These may include sequestration in the enlarged spleen and reduced thrombopoietin production by the diseased liver (Table 1). The role of antiplatelet antibodies has also been alluded to in the genesis of liver disease related thrombocytopenia[5]. Antibodies may also account for thrombocytopenia associated with viral hepatitis[6,7]. The improvement in thrombocytopenia after liver transplantation has been ascribed to the normalization of thrombopoietin production[8].

The incidence of thrombocytopenia in chronic hepatitis C is higher than the general population and variable incidence (0.16%-45%) has been reported from multiple reports[1,7,9,10]. The reason is that different definitions have been used to define thrombocytopenia and different disease stage of liver disease of included patients. A report indicated that the likelihood of having a platelet count of less than 100000/mm^3 was 12 in the cirrhotic population vis-à-vis the general population[10]. Indeed thrombocytopenia is considered an indirect marker of severity of chronic liver disease and may predict the presence of cirrhotic complication especially esophageal varices[11,12]. In fact a ratio of platelet to spleen size may help predict the presence of esophageal varices in patients with liver disease[12]. Thrombocytopenia of liver disease is usually not life-threatening. The importance of liver disease related thrombocytopenia relates to the difficulties in management of such patients including in administration of antiviral therapy in hepatitis C virus (HCV), or the difficulty in doing invasive procedures in chronic liver disease[2,13]. Most importantly low platelet counts are a contraindication to start pegylated interferon related therapy in patients with HCV infection. Interferon itself causes thrombocytopenia in around 30%-35% of patients[14,15]. In spite of recent advances in management of HCV and number of interferon free regimens becoming available, interferon remains a therapy of first choice in many countries due to the lack of availability and high costs of the newer regimens[16].

Traditionally many treatment options were available for management of liver disease related thrombocytopenia but these were either invasive or had significant risks associated with them. Platelet transfusion remained the standard especially in emergent settings but with the caveat that there were attendant risks of transfusion transmitted infections, febrile reactions, lung injury and alloimunisation[17]. Other options included splenectomy or splenic artery embolization with an intent to reduce the effects of hypersplenism to raise thrombocyte counts[2]. Danazol, in a dosage of 300-600 mg daily has also been found effective for management of thrombocytopenia in chronic hepatitis C thereby enabling administration of antiviral therapy with pegylated interferon and ribavirin[18]. However the availability of thrombopoietin agonists has remarkably altered the management of liver disease related thrombocytopenia.

THROMBOPOIETIN AGONISTS

Formation of platelets is a complex process wherein pleuripotent hematopoietic stem cells undergo maturation to form the megakaryocytes. The production of megakaryocytes is controlled and can increase ten folds in times of need[19]. This increase involves regulation by many factors including interleukin (IL)-3, IL-6, IL-11 and most importantly thrombopoietin. Although its existence was postulated in 1958, thrombopoietin (TPO) was discovered in 1994 by five different laboratories independently[20]. TPO is synthesized in the liver and mediates its actions through interaction with Human anti-thrombopoietin receptor receptor resulting in downstream activation of various signaling pathways like janus kinase/signal transducer and activator of transcription, Shc/Ras/mitogen-activated protein kinase and phosphatidylinositol 3-kinase/Akt which result in activation and proliferation of erythroid, myeloid and megakaryocytic progenitors. Therefore, TPO has been also termed as a pan-hematopoietic cytokine[21].

Discovery of TPO and its effects on megakaryocyte proliferation resulted in efforts to use TPO and its congeners in clinical situations. Two recombinant thrombopoietins entered clinical development: recombinant full length thrombopoietin (rhTPO) and pegylated recombinant human megakaryocyte growth and development factor (PEG-MGDF). The essential difference between the two is whilst rhTPO is a full length glycosylated form of TPO, PEG-MGDF is a truncated and non-glycosylated form of TPO[22]. Both these agents were effective in elevating platelet counts and were used in various clinical indications. rhTPO resulted in elevation in platelet counts from day 4 to day 21 of administration with peak levels on day 12[23]. Pharmacokinetics with PEG-MDGF were also similar. However further clinical development of these otherwise excellent drugs was halted because of development of neutralizing antibodies especially with PEG-MDGF[24,25]. However the second generation of thrombopoietin agonists soon entered clinical realm and have since added to the armamentarium available for management of immune thrombocytopenia and other thrombocytopenic disorders. Romplostim is a peptibody which was synthesized by combining a pair of 14 amino

acid TPO peptide into IgG type 1 heavy chain resulting in a drug with significant with potent action on megakaryocyte production[26]. Romiplostim is used as once in a week subcutaneous injection[20,27]. Since romiplostim has no molecular homology with the human TPO, no problem of neutralizing antibodies has been noted with its use[26]. Eltrombopag is the other second generation molecule which is orally active and is a biaryl hydrazone[27,28].

ELTROMBOPAG

Eltrombopag is a non-peptide TPO agonist which acts on the thrombopoietin receptor to increase the production of platelets. It was first approved in 2008 for treatment of immune thrombocytopenia. Since then its role has been recognized in management of thrombocytopenia of diverse etiologies[19,27,29]. Being structurally different from the endogenous TPO, the interaction with TPO receptor is non-competitive and additive[30]. In relapsing or refractory immune thrombocytopenia, eltrombopag was seen to exhibit a dose dependent increase in platelet counts over doses of 30, 50 and 75 mg/d[31]. The dosages available are 12.5, 25, 50, 75 and 100 mg. In immune thrombocytopenia the lowest dosage which achieves a platelet count of 50000/μL is used. Use of higher doses in chronic liver disease may predispose to more chances of portal vein thrombosis. In such a situation an initial dosage of 25 mg/d for 2 wk has been recommended[32]. Certain precautions need to be observed whilst prescribing eltrombopag. The drug must be taken empty stomach with a 1-2 h interval between the drug intake and the meals. Concomitant calcium supplements or other polyvalent cations must be avoided and the patient must not take the drug more than once in a 24 h period. In a pharmacokinetic study in healthy volunteers it was noted that intake of calcium or magnesium and aluminum containing antacids reduced the systemic availability of the drug[33].

Eltrombopag is absorbed to the extent of around 50% after oral ingestion and peak plasma levels are achieved in 2-6 h[27]. Twenty percent of the drug is excreted unchanged in faeces[34]. With increasing hepatic impairment the area under curve increased suggesting that liver plays an important role in elimination of eltrombopag[35]. Eltrombopag also has low-distribution performance and liver is the primary site for its distribution and elimination both[34]. Apart from immune thrombocytopenia eltrombopag has also been used in myelodysplastic syndrome, chemotherapy related thrombocytopenia, and aplastic anemia[19]. Eltrombopag is a fairly safe drug. The most common side effects noted include headache, malaise, fever, deranged liver function tests including transaminase elevations and indirect hyper-bilirubinemia[36,37]. Other reported adverse events include cutaneous hyperpigmentation, erythroderma, pruritic exanthema and episodes of venous thrombosis at various sites[37-39]. Although increased cataracts had also been reported but patients had received steroids for immune thrombocytopenia[37]. Possible reasons for stopping eltrombopag treatment include severe adverse events like thrombosis, lack of response to maximal dose for 4 wk, or elevation in transaminases more than three folds of the baseline[40].

ELTROMBOPAG IN HEPATITIS C THERAPY

Therapy for HCV has been an area of much contemporary interest and has seen many new drugs emerge which are likely to become available globally and will result in increased rates of sustained virologic response and reduced side-effects[41]. Interferon free regimens are now a clinical reality for all HCV genotypes[42]. The combinations of ledipasvir and sofosbuvir given for a 12 wk duration provide standard variable rate (SVR) of more than 90% in HCV genotype 1[43,44]. Even for genotype 2 and 3 a combination of sofosbuvir and ribavirin for 12 and 24 wk respectively provides good SVR rates[45,46]. However pegylated interferon and ribavirin combination remains the therapy of choice for many patients due to issues of affordability and availability of the newer agents.

As previously discussed HCV is known to cause thrombocytopenia. It may also increase the risk of developing immune thrombocytopenia[47,48]. The matter is further complicated in the patients receiving pegylated interferon and ribavirin. Interferon is known to cause thrombocytopenia by causing bone marrow suppression[49]. In a large report on interferon therapy in HCV patients, baseline thrombocytopenia was present in 44% of patients. In patients with severe thrombocytopenia (< 75000/μL), the need to stop interferon or reduce its dose was much higher. Severe bleeding events were uncommon but a platelet count of < 50000/μL predicted an increased risk of bleeding[50].

ENABLE-1 and 2 trials provided data regarding use of eltrombopag to ensure initiation and completion of interferon and ribavirin therapy (Table 2). In ENABLE-1 trial patients with HCV infection and platelet count of < 75000/μL received progressively increasing doses of eltrombopag (25, 50, 75 and 100 mg) to achieve a platelet count of > 90000/μL. With this strategy initiation of interferon treatment was possible in 95% cases and only in 2% cases did the count not increase to the desired level. Also 88% patients benefited with a dose of 50 mg/d or less. The group was now randomized to either receive pegylated interferon-2a and ribavirin with placebo *vs* with eltrombopag. Although the rates of RVR were similar in the two groups the rates of EVR and SVR were increased in those receiving eltrombopag. Dose reductions of interferon were higher in the placebo arm. ENABLE-2 had a similar study design except for the use of pegylated interferon 2b instead of 2a used in ENABLE-1. The results were similar with 96% patients achieving the target platelet counts. Median time to achieve the target was 2 wk. Discontinuations were higher with the placebo arm but thromboembolic events including portal vein thrombosis

Table 2 Studies of Eltrombopag in patients with liver disease

Ref.	Population	Type	Results
McHutchison *et al*[55]	Compensated HCV cirrhosis with thrombocytopenia	Phase Ⅱ RCT, placebo controlled	Dose dependent increase noted with eltrombopag
Kawaguchi *et al*[32]	Cirrhosis	Phase Ⅱ Randomised Open label study	Risk of thrombotic phenomenon, recommends lower dose in Japanese
Afdhal *et al*[56] ELEVATE trial	Cirrhosis patients, periprocedural use	Phase Ⅲ, RCT, placebo controlled	Decreased platelet transfusion with eltrombopag with increased risk of portal vein thrombosis
Afdhal *et al*[51] ENABLE 1 and 2 trial	HCV related thrombocytopenia, to enable SVR	Phase Ⅲ, RCT, placebo controlled	Decreased dose reduction in eltrombopag group, Higher SVR

HCV: Hepatitis C virus; SVR: Standard variable rate.

were higher in the eltrombopag arm as were the rates of hepatic decompensation[51-53]. The occurrence of portal vein thrombosis may compromise the feasibility and outcomes of liver transplantation which may be needed in these patients. Interestingly neither the dosage of eltrombopag nor the platelet counts predicted the risk of thromboembolic events in the ENABLE trials[49]. With advent of interferon free therapies, the use of eltrombopag or other thrombopoietin agonists for enabling interferon based therapies is likely to decrease in the near future. However, there is still time before the majority of world population especially in the low income countries has access to direct acting antivirals and till that time role of eltrombopag to support difficult to treat groups like those with cirrhosis will remain[54].

ELTROMBOPAG IN CIRRHOSIS

Compensated cirrhosis with HCV is also an indication for treatment with interferon but the presence of thrombocytopenia complicates the management. In a trial evaluating multiple dose regimens of eltrombopag for management of thrombocytopenia in HCV related cirrhosis so as to initiate interferon and ribavirin therapy, 74 patients were assigned to receive placebo, 30, 50 or 75 mg of eltrombopag daily for 4 wk. Twelve weeks therapy with the antivirals was possible only in 6% patients receiving placebo whilst a progressively larger number of patients (36%, 53%, and 65%) were able to receive therapy with increasing doses of eltrombopag (30, 50, and 75 mg respectively)[55]. In this trial three patients required withdrawal of eltrombopag for various reasons including new onset ascites, retinal exudates and neutropenia; effects not entirely related with use of eltrombopag. Further information on use of eltrombopag in cirrhosis came from the ELEVATE trial in which patients with cirrhosis and a platelet count of < 50000/μL who were planned for an invasive procedure received either placebo or eltrombopag in a dosage of 75 mg daily for 2 wk before the planned procedure (Table 2). In a significantly higher number of patients receiving the drug (72%) vis-à-vis the placebo (19%), the transfusion of platelets could be avoided. However, there were no differences in significant bleeding episodes[56]. This, however, came at an increased risk of portal vein thrombosis in the treatment arm raising concerns about the safety. Interestingly the dosage used in this trial was a higher one at 75 mg and the risk increased with higher platelet count levels[56,57]. There are reports suggesting a higher drug exposure in East Asian population and lower initial doses have been recommended[58,59]. In a report from Japan on 38 patients with chronic liver disease even a dosage of 12.5 mg daily resulted in a mean platelet elevation of 24000/μL suggesting that lower doses may be effective in this population. More side effects as also serious events like portal vein thrombosis were noted in the 37.5 mg group[32]. Other case reports have also described similar events with the usage of eltrombopag or romiplostim in chronic liver disease[60,61]. Romiplostim has also been effective for management of HCV and cirrhosis related thrombocytopenia[62,63]. The use of romiplostim was reported to be effective in raising the platelet count in majority of patients (33 out of 35) with chronic hepatitis C related cirrhosis to a level of > 70000/μL thereby enabling surgical procedures. No major bleeding or thrombotic episodes were reported in this Phase Ⅱ study[64,65].

CONCLUSION

Eltrombopag is effective in treatment of thrombocytopenia of liver disease and may help in certain clinical situations. The drug may be of use to initiate and complete interferon based anti-HCV therapy and may have a role prior to invasive procedures in patients with cirrhosis. However the use must be tempered by the possible risk of thrombotic complications including portal vein thrombosis. Importantly the minimum possible dose which can achieve the requisite platelet count should be used.

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