

The role of eltrombopag in the management of hepatitis C virus-related thrombocytopenia

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Abstract: Eltrombopag is a 2nd generation thrombopoietin-receptor agonist. It binds with the thrombopoietin-receptors found on the surfaces of the megakaryocytes & increases platelet production. Many recent studies have suggested a potential role for this novel agent in the treatment of thrombocytopenia associated with hepatitis-C infection. Studies have shown that adjunct treatment with Eltrombopag can help avoid dose reductions/withdrawals of pegylated interferon secondary to thrombocytopenia. It may also have a role in priming up platelet levels to help initiate antiviral therapy. Similarly, chronic liver disease patients with thrombocytopenia who need to undergo an invasive procedure may be potential candidates for short two-week courses of eltrombopag in the peri-procedural period to help reduce the risk of bleeding. Besides the price (deemed very expensive and probably not cost-effective), there are some legitimate concerns about the safety profile of this novel agent (most importantly, portal vein thrombosis, bone marrow fibrosis and hepatotoxicity). In this article, the potential role of eltrombopag in the context of hepatitis C virus (HCV)-related thrombocytopenia is reviewed. To write this article, a MEDLINE search was conducted (1990 to November 2012) using the search terms “eltrombopag,” “HCV,” and “thrombocytopenia.”

Keywords: liver disease, chronic immune thrombocytopenic purpura, thrombopoietin-receptor agonist, romiplostim

Hepatitis C virus-related thrombocytopenia

Hepatitis C virus (HCV) infection is estimated to have chronically infected 160 million individuals worldwide.¹ HCV is known to cause thrombocytopenia even in the absence of overt hepatic disease^{2,3} and is considered a surrogate marker for the severity of liver disease.⁴ It is sometimes the *only* manifestation of viral hepatitis. Chiao et al suggested that HCV infection is associated with an increased risk of developing chronic immune thrombocytopenic purpura (CITP) (hazard ratio, 1.8; 95% confidence interval [CI], 1.4–2.3).⁵ Similarly, Pockros et al retrospectively estimated that the prevalence of CITP among their HCV patients was much greater than would be expected by chance ($P < 0.00001$).⁶ Conversely, many cross-sectional studies have reported positive HCV serology (up to 20%) in patients with a clinical diagnosis of CITP.^{7,8} The documented severity of thrombocytopenia in different studies has been highly variable, ranging from mild to severe.

Thrombocytopenia is a well-known relative contraindication for the initiation of antiviral therapy in HCV-infected patients and may also result in the postponement of many invasive procedures that chronic liver disease (CLD) patients may need to undergo, such as percutaneous, transjugular, or laparoscopic liver biopsy; paracentesis;

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thoracentesis; radiofrequency ablation; or partial hepatectomy for hepatocellular carcinoma. The latter group of patients may also need to undergo splenectomy, especially if the platelet counts are $<50,000/\text{mm}^3$.

Mild ($>75,000$ to $<150,000/\text{mm}^3$) to moderate ($50,000$ – $75,000/\text{mm}^3$) thrombocytopenia is only rarely associated with any bleeding complications. However, undertaking invasive procedures in the background of severe thrombocytopenia ($<50,000/\text{mm}^3$) may be associated with significant morbidity necessitating repeated platelet transfusions in the perioperative period.^{9–11} Platelet transfusions are generally effective for only a few hours; moreover, they may be associated with multiple potential complications – such as febrile nonhemolytic and allergic reactions, platelet refractoriness (due to human leukocyte antigen alloimmunization), and iron overload (with chronic repeated transfusions) – and the potential need for hospitalization, risk of infection, and treatment cost can also be of concern.^{11,12} This explains the need and rationale for an alternative therapeutic option to help raise platelet counts when needed. Different therapeutic strategies have been suggested and tried for the treatment of HCV-related thrombocytopenia in different studies with variable success (generally disappointing).¹³ However, the recent introduction of second-generation thrombopoietin-receptor agonists (TPO-RAs) has opened up a novel way to treat thrombocytopenia. In 2008, the US Food and Drug Administration approved two TPO-RAs – eltrombopag and romiplostim – for use in CITP patients refractory to at least one standard treatment.

The cause–effect relationship between HCV infection and thrombocytopenia

In areas of high HCV seroprevalence, it is generally recommended that if a patient presents with thrombocytopenia and has one or more risk factors for HCV, they should be screened for the virus.^{14,15} Important risk factors that should prompt checking for HCV status include having had needle stick injury or mucosal exposure to HCV-positive blood, intravenous drug abuse, having had multiple blood transfusions and/or hemodialysis, being a current sexual partner of an HCV-infected person or having multiple sexual partners, being a child born to an HCV-infected mother, and having unexplained abnormal aminotransferase levels.

Multiple studies have demonstrated significant improvements in platelet counts following successful treatment of HCV infection, suggesting that the latter may be a cause of thrombocytopenia.^{16,17} In fact, several studies have suggested that thrombocytopenia is found in as much as 76%

of cases of cirrhosis of liver.^{9,18,19} The severity of thrombocytopenia is generally directly proportional to the severity of the CLD.^{20,21} Although thrombocytopenia is generally less severe in HCV-infected patients than in CITP patients, the former are more prone to major bleeding episodes due to liver disease-associated coagulopathy and portal hypertension. Interestingly, a recent study suggested that it is thrombocytopenia rather than coagulopathy that is the major determinant of bleeding risk in patients with CLD.²² The same study estimated the bleeding incidence to be 31% in patients with platelet count $<75,000/\text{mm}^3$. The World Health Organization (WHO) classifies bleeding into grade 1 (petechiae), grade 2 (mild blood loss), grade 3 (gross blood loss), and grade 4 (debilitating/life-threatening blood loss).²³

Possible causes for HCV-related thrombocytopenia include:

- *Decreased platelet production*, which could be due to decreased hepatic production of thrombopoietin (TPO) (a glycoprotein that promotes megakaryopoiesis)^{24,25} and direct suppressant effect of HCV on bone marrow.^{26,27}
- *Increased peripheral destruction of platelets*, which could be due to immune-mediated peripheral platelet destruction⁶ and hypersplenism leading to increased splenic platelet sequestration.^{28,29} Since HCV is known to cause thrombocytopenia even in well-compensated cases (in the absence of portal hypertension and hypersplenism)^{8,16} and thrombocytopenia has been shown to persist after portal decompression in established cases of hypersplenism (decompensated cirrhotics),³⁰ it appears that immune-mediated destruction of platelets is a more dominant mechanism of thrombocytopenia than hypersplenism. The binding of HCV to platelet membranes and the consequent anti-HCV antibody binding and platelet phagocytosis (called “innocent bystander” phagocytosis)³¹ and the mimicking of an epitope by the HCV protein GPIIIa on the platelet surface that triggers the production of antiplatelet antibodies³² are the two most frequently postulated immune mechanisms explaining increased peripheral platelet destruction in HCV-infected cases.^{6,26,31,33}
- *Iatrogenesis*. Interferon (IFN) therapy is known to suppress bone marrow, resulting in a 10%–50% fall in platelet count.²⁴ Polyethylene glycol (PEG)-ylated IFN/ribavirin (RBV) combination therapy has been shown to cause more severe thrombocytopenia than non-PEGylated IFN/RBV combination therapy. Interestingly, thrombocytopenia is worst with PEG-IFN monotherapy,³⁴ suggesting that concomitant RBV therapy probably has some protective effect (causes reactive thrombocytosis).²⁴

In one study, PEG-IFN therapy-induced thrombocytopenia led to dose reductions in 19% of cases and discontinuation in 2% of cases.³⁵ In cirrhotic patients, the incidence of treatment-induced thrombocytopenia is generally higher than in non-cirrhotic patients.¹⁹

Interestingly and paradoxically, advanced liver disease patients, such as cirrhotics, are not only predisposed to bleeding (secondary to thrombocytopenia and coagulopathy) but also to thromboembolic events (TEEs), especially portal/splenic vein thrombosis. Reduced portal vein flow and possible presence of intra-abdominal cancer are two pertinent predisposing factors for the development of TEEs in such patients.^{36–38} Performance of an invasive procedure in cirrhotics and hepatocellular carcinoma patients is also considered an independent risk factor for the development of portal vein thrombosis (incidence estimated to be up to 35%).^{39,40} In particular, it appears that patients who undergo an invasive procedure involving splanchnic circulation (eg, variceal banding, radiofrequency ablation, or transarterial chemoembolization) are especially vulnerable to developing portal/splenic vein thrombosis.⁴¹

Pathophysiology of TPO

TPO, a glycoprotein primarily produced by hepatocytes, is the major regulator of both megakaryopoiesis and platelet production in the human body. It is the key endogenous ligand for the TPO receptor (TPO-R) found on the surface of megakaryocytes and megakaryocytic precursors.^{42,43} The binding of TPO to its receptor activates the Janus kinase/Signal Transducer and Activator of Transcription pathway, ultimately leading to the release of platelets in the circulation.^{44–46} TPO also binds to circulating platelets, enhancing their activation and function.

Platelets not only bind to TPO but also internalize and degrade it. Thus, if the platelet count increases, TPO degradation also increases and vice versa. This negative feedback system helps maintain normal platelet levels. In liver cirrhosis, the net production of TPO decreases, thus predisposing to thrombocytopenia.^{25,47} Studies have shown that the grade of liver fibrosis, the severity of TPO deficiency, and the incidence of thrombocytopenia are all positively correlated.²⁵ Correction of TPO deficiency by liver transplant has been shown to improve megakaryopoiesis and thus circulating platelet levels.^{48,49}

Treatment

Since successful treatment of HCV infection has clearly been shown to improve the platelet count,^{6,50} the therapeutic

protocol for managing HCV-related thrombocytopenia ought to differ from that for primary (idiopathic) thrombocytopenic purpura. Therapeutic strategies employed in different studies to treat HCV-related thrombocytopenia have included: first-generation thrombopoietic growth factors,^{51–54} IFN dose reduction;⁵⁵ the addition of a new drug – such as an oral steroid^{8,16,56,57} – intravenous immunoglobulin (Ig)⁷ or anti-RhD Ig;¹⁵ and invasive procedures such as partial splenic embolization,⁵⁸ splenectomy,^{8,16} or transjugular intrahepatic portosystemic stent shunt placement.

In the past, multiple clinical trials demonstrated improvements in platelet counts with first-generation thrombopoietic growth factors (recombinant human TPO and PEGylated recombinant human megakaryocyte growth and development factor [PEG-rHuMGDF]).^{51–54} However, their use was discontinued in 1998 when some patients paradoxically developed thrombocytopenia secondary to PEG-rHuMGDF use.^{59–62} The possible explanation given was development of anti-PEG-rHuMGDF antibodies, which cross-reacted and thus neutralized the endogenous TPO. This led to efforts to develop non-immunogenic second-generation TPO-RAs – romiplostim (AMG-531; Nplate[®], Amgen, Thousand Oaks, CA, USA) and eltrombopag (SB-497115; Promacta[®] and Revolade[®], GlaxoSmithKline, London, UK).⁶³

Although steroids are commonly used in CITP patients, their use in HCV-infected patients has been shown to cause statistically significant rises in transaminase levels and HCV viral loads and result in worsening of liver damage.¹⁵ They have even been shown to cause hyperbilirubinemia and, rarely, development of overt jaundice.¹⁵ Because of these safety issues, steroid use in the treatment of HCV-related thrombocytopenia has never gained recognition, despite conflicting reports of variable increases in platelet count. Based on this, it is recommended that all patients who are suspected of suffering from CITP be investigated for hepatitis C serology. This recommendation will hopefully prevent the potential adverse effect of prolonged corticosteroid usage on the underlying infection, if present.

Splenic artery embolization and splenectomy are often effective in increasing platelet levels in patients with portal hypertension regardless of hepatitis C serology status;^{8,16} however, these may be associated with such complications as splenic abscesses and portal vein thrombosis. Portal decompression with transjugular intrahepatic portosystemic stent shunt placement may or may not improve platelet levels because of the multifactorial pathogenesis of the latter.^{30,64}

The American Society of Clinical Oncology recommends platelet transfusions for cancer patients with platelet counts

of 10,000–20,000/mm³.⁶⁵ The American Society of Hematology (ASH) suggests that in idiopathic thrombocytopenic purpura patients without other risk factors, platelet levels of 30,000–50,000/mm³ are required to preclude most serious bleeding (intracerebral or major gastrointestinal) complications.⁶⁶ No consensus currently exists regarding the appropriate cut-off level of thrombocytopenia below which platelet transfusions may be indicated prophylactically in CLD patients. It appears that the appropriate cut-off value should be different in different patients. In uncomplicated thrombocytopenic patients, a cut-off value of <10,000/mm³ may be considered appropriate, whereas in complicated thrombocytopenic patients (eg, those with fever, infection, splenomegaly), a higher cut-off value such as <50,000/mm³ should be regarded as appropriate^{67,68} (platelet levels of ≥50,000/mm³ are often considered safe for most invasive procedures).^{69,70}

The most practical strategy for treating HCV-related thrombocytopenia is based on the hypothesis that eradicating the HCV infection should result in remission of thrombocytopenia. A pretreatment platelet count of <90,000/mm³ is a relative contraindication to commencing PEG-IFN therapy.⁷¹ If the pretreatment platelet level is above this cut-off value, and thrombocytopenia develops following initiation of PEG-IFN therapy, one treatment option may be to continue PEG-IFN therapy but to reduce its dose (minimum effective dose is 1 µg/kg/week) if the platelet count is <30 × 10⁹/L, or to discontinue it if the platelet count is <20 × 10⁹/L.^{55,72} Reductions in the dosage schedule of PEG-IFN can compromise the success of the therapy. To help maintain an optimal dosage schedule, adjunct eltrombopag (or romiplostim) may be considered to counteract thrombocytopenia in a sustained manner.^{73,74}

Recently, the manufacturer of eltrombopag, Amgen, conducted an indirect comparison between eltrombopag and romiplostim in CITP.⁷⁵ The aim was to evaluate the relative effectiveness of the two drugs in terms of platelet response and bleeding adverse event rates using placebo as the common comparator. The results showed no significant differences between the two drugs in terms of achieving either durable/sustained platelet responses, or overall platelet responses in all patients (splenectomized or non-splenectomized). Similarly, no significant differences in the incidence of bleeding adverse events (WHO grade 2 or higher) were noted.

Eltrombopag is already recommended for CITP patients in two scenarios: (1) post-splenectomy, when patients are refractory to other drug therapies (eg, corticosteroids, Igs), and (2) when splenectomy is contraindicated and other

medical agents have failed to correct the thrombocytopenia. The drug has recently been used successfully in two cases of persistently thrombocytopenic, platelet transfusion-dependent patients following stem-cell transplantations (one allogeneic and one autologous).⁷⁶ In both cases, the patients became platelet-transfusion independent with a platelet count of ~30,000 and ~10,000/mm³, respectively, within ~2 weeks of starting eltrombopag treatment. It is pertinent to mention that the usefulness of repeated platelet transfusion is limited because they have a short duration of efficacy, there is risk of transfusion-related reactions, and there is an almost 50% incidence of alloimmunization (development of antiplatelet antibodies leading to refractory thrombocytopenia nonresponsive to repeat platelet transfusions).^{77–79} Thus, it appears that the therapeutic indications of eltrombopag may expand in the coming years (provided the drug proves relatively safe in human subjects, and the cost is not inhibitive).

Eltrombopag treatment

Treatment aim

The ultimate aim of treating thrombocytopenia in HVC-positive patients is not to normalize the platelet count⁸⁰ but to maintain it above the level of hemorrhagic risk (>50,000/mm³), thus the possibility of being able to avoid reducing or interrupting IFN treatment.

Mechanism of action

Eltrombopag is a TPO-RA.^{81–82} The ligand-receptor binding activates the Janus kinase/Signal Transducer and Activator of Transcription signaling pathway, inducing increased proliferation and differentiation of human bone marrow progenitor cells into megakaryocytes. The net effect is an increase in the circulating platelet count. It appears that eltrombopag binds the TPO-R at a distance from the binding site for endogenous TPO and appears to initiate signal transduction by a different mechanism.⁸³ Thus, the two may have an additive (rather than competitive) effect on platelet production. Endogenous TPO appears to be seven to nine times more potent than eltrombopag.

Pharmacokinetics

It appears that the pharmacokinetics of eltrombopag (peak concentration 2–6 hours after oral administration; average half-life > 12 hours) is linear, therefore it produces a dose-dependent increase in platelet proliferation and differentiation (higher doses are more effective and less safe).^{82,84–87} Eltrombopag should be taken at least 4 hours before or after antacids, dairy products, and multivitamin tablets/mineral

supplements, as these products chelate and thus significantly reduce the systemic absorption of eltrombopag.⁸⁸ Although the absolute oral bioavailability of eltrombopag in human subjects has not been well established, it is estimated to be at least 52%. Almost all (99.9%) absorbed eltrombopag circulates bound to plasma proteins, predominantly albumin. Circulating eltrombopag undergoes extensive hepatic metabolism through cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or cysteine.

Since individual uridine diphosphate-glucuronosyltransferase (UGT) enzymes only show a limited contribution in the glucuronidation of eltrombopag, significant drug interactions involving glucuronidation are not anticipated with this drug. Further, eltrombopag does not appear to inhibit or induce cytochrome P450 (CYP) enzymes in both in vitro and in vivo studies. This implies that no clinically significant interactions should be expected when eltrombopag and CYP inducers or inhibitors are coadministered.

Since eltrombopag is primarily metabolized in the liver, higher plasma eltrombopag concentrations are reported in HCV-infected patients than in CITP patients or healthy volunteers.⁸⁹

Interethnic differences in the pharmacokinetics of eltrombopag have also been reported. It is suggested that low-dose 25 mg once-daily eltrombopag therapy suffices in most patients of Asian origin (compared with in Caucasians, who usually require double this dose).⁹⁰ The underlying mechanism accounting for the observed interethnic difference in the pharmacokinetics of eltrombopag is not clear; nonetheless, the most plausible explanation appears to be the difference in the body weight (less in East Asian population compared with the general Caucasian population).⁹¹ Since the clearance of eltrombopag increases with increase in body weight,⁹² heavy subjects need higher doses to produce an identical therapeutic effect. Another possible explanation is the known interethnic differences^{92,93} in the levels of activities of different drug metabolizing enzymes involved in eltrombopag metabolism (eg, CYP1A2, CYP2C8, UGT1A1, and UGT1A3).⁹¹ The predominant route of eltrombopag excretion is via feces (59%) followed by urine (31%). Via the latter, only metabolites (and not the parent drug) have been found to be excreted.⁹⁴

Therapeutic efficacy

The evidence of the effectiveness of eltrombopag primarily comes from two Phase III randomized double-blind placebo-controlled trials on CITP patients.

In a recent Phase III randomized double-blind placebo-controlled study,⁹⁵ 197 CITP patients were randomized

2:1, eltrombopag (n = 135) to placebo (n = 62). Median platelet count at baseline was 16,000/mm³ in both groups. The study showed that whereas only 17 (28%) patients in the placebo group responded to treatment, the treatment response (at least once during the study) was much higher in the eltrombopag group (106, ie, 79% patients). The odds of responding were demonstrated to be greater in the eltrombopag group compared with the placebo group throughout the 6-month treatment period (odds ratio [OR], 8.2; 99% CI, 3.59–18.73; *P* < 0.0001). A platelet count between 50,000 and 400,000/mm³ in the absence of rescue medication (steroids, Ig) was achieved by significantly more patients in the eltrombopag-treated group during the 6-month treatment period (*P* < 0.001). This rise in platelet count resulted in an approximately 50% reduction in the incidence of clinically significant bleeding (WHO grades 2–4) from day 15 to the end of treatment.

In another Phase III randomized double-blind placebo-controlled study,⁹⁶ CITP patients with platelet counts of <30,000/mm³ were given eltrombopag 50 mg once daily (n = 76) or placebo (n = 38) for up to 6 weeks. The target was to achieve platelet counts of ≥50,000/mm³ at day 43. While only 16% of the patients receiving placebo achieved the target platelet count, 59% of eltrombopag-treated patients achieved the target (OR, 9.61 [95% CI, 3.31–27.86]; *P* < 0.0001). Moreover, the eltrombopag-treated patients had fewer instances of bleeding complications at any given time during the study than the placebo group (OR, 0.49 [95% CI, 0.26–0.89]; *P* = 0.021).

In a Phase II clinical trial,⁹⁷ while only 6% of HCV-related cirrhotics in the placebo group completed the 12-week antiviral course, the same was completed by 36%, 53%, and 65% of patients receiving 30, 50, and 75 mg of eltrombopag, respectively. Moreover, 75%–95% of patients in the eltrombopag groups achieved the primary endpoint of a platelet count 100,000/mm³ at week 4, in a dose-dependent manner. During this study, seven patients reported serious adverse effects. In patients receiving 50 mg of eltrombopag, one patient developed myositis, and one neutropenia. Thrombocytopenia was reported in one patient (originally receiving 30 mg of eltrombopag) after discontinuing eltrombopag and starting peginterferon therapy. Thrombocytopenia was thus thought to be peginterferon-related, rather than eltrombopag-related. Ascites were reported in the group receiving 30 mg of eltrombopag and led to the withdrawal of eltrombopag in three patients. The ascites resolved subsequently. Retinal exudates were reported in the group receiving 75 mg of eltrombopag and led to the withdrawal

of eltrombopag in one patient. The retinal exudates failed to subsequently resolve and the investigators were of the view that these were unrelated to eltrombopag therapy.

In a recent double-blind randomized placebo-controlled Phase III clinical trial conducted in 13 countries (the ELEVATE study),⁹⁸ 292 patients with CLD due to variable causes and with associated thrombocytopenia (platelet count $< 50,000/\text{mm}^3$) were randomly assigned to receive either eltrombopag (75 mg daily) or placebo for 14 days before a planned invasive procedure (last dose ~5 days before the procedure).⁴¹ Avoidance of platelet transfusion before, during, and up to 7 days after the procedure was set as the primary endpoint. The primary endpoint was successfully achieved in 72% (104/145) patients in the eltrombopag group compared with only 19% (28/147) in the placebo group ($P < 0.001$). Bleeding episodes of WHO grade 2 or higher were reported in 17% and 23% of patients in the eltrombopag and placebo groups, respectively. Importantly, this study showed the development of portal venous thrombosis in six patients receiving eltrombopag, whereas only one developed this in the placebo group.

Ten TEEs were recorded in eight patients – seven events in the eltrombopag group (OR, 3.04; 95% CI, 0.62–14.82) and three in the placebo group. All events occurred 1–38 days after cessation of eltrombopag or placebo therapy. Nine of the ten TEEs involved symptomatic portal or splenic vein thrombosis – all occurring in the eltrombopag group; the remaining TEE, which occurred in the placebo group, was a myocardial infarction (MI). All affected patients in the eltrombopag group except one developed a TEE at a platelet level of $\geq 200,000/\text{mm}^3$. Post hoc analysis confirmed an association between a platelet level of $\geq 200,000/\text{mm}^3$ and increased risk of portal venous thrombosis. The study concluded that until more data is available from further studies on the safety profile of eltrombopag, the drug is *not* recommended as an alternative to platelet transfusion in CLD patients (with thrombocytopenia) undergoing invasive procedures.

In another recent randomized open-label Phase II study,⁹⁹ twelve CLD patients with platelet counts $< 50,000/\text{mm}^3$ received 12.5 mg eltrombopag once daily for 2 weeks. After evaluating the safety of the drug, in the second part of the study, 26 patients were randomly assigned to receive either 25 or 37.5 mg eltrombopag once daily for 2 weeks. At week 2, the mean increases in the platelet counts from the baseline were $24,800/\text{mm}^3$ (95% CI, 8200–41,400), $54,000/\text{mm}^3$ (95% CI, 28,200–79,800), and $60,000/\text{mm}^3$ (95% CI,

29,300–90,700) in the 12.5, 25, and 37.5 mg groups, respectively. Most side effects were grade 1 or 2. Two patients in the 37.5 mg group developed serious side effects. It was therefore recommended that eltrombopag 25 mg daily is effective in alleviating thrombocytopenia in CLD patients.

The safety and efficacy of long-term use of eltrombopag has been tested recently in the interim analysis¹⁰⁰ of the ongoing global multicenter open-label EXTEND study of 299 CITP patients treated for up to 3 years.¹⁰¹ The results showed that a platelet level of $\geq 50,000/\text{mm}^3$ was achieved at least once in both splenectomized and non-splenectomized patients (80% and 88%, respectively, for a median of 73/104 and 109/156 cumulative study weeks, respectively). Seventy percent or more of patients who previously failed to respond or relapsed after either rituximab therapy or splenectomy achieved the target platelet level of $\geq 50,000/\text{mm}^3$ at least once. The same target was achieved for $>50\%$ of study visits in almost 50% of patients who had been treated with four or more prior idiopathic thrombocytopenic purpura treatments. Bleeding symptoms (WHO grades 1–4) decreased from a baseline of 56% to 20% at 2 years and 11% at 3 years, reflecting the inverse relationship between platelets and bleeding severity in CITP patients.⁷⁰ Thirteen percent of patients experienced one or more adverse events leading to study withdrawal. Six of these patients withdrew due to hepatotoxicity. The interim analysis concluded that long-term treatment with eltrombopag is effective in achieving and maintaining target platelet levels and that the drug is well tolerated and generally safe.

Criteria for commencing eltrombopag therapy

There are three criteria.

1. Thrombocytopenia is the underlying cause in almost 6% cases of PEG-IFN dose reductions or withdrawals.³⁴ Thus, in an HCV-positive patient on antiviral therapy, eltrombopag therapy should be considered if their platelet count falls to $< 50,000/\text{mm}^3$ and their Child–Pugh score is < 5 and detailed history and examination suggests a realistic risk of bleeding. If their Child–Pugh score is ≥ 5 , it is better to avoid eltrombopag or use it only when the benefits clearly outweigh the risks – in which case treatment should be actively monitored (in the recent Phase II Japanese study,⁹⁹ a Child–Pugh score ≤ 9 – ie, Child–Pugh classes A and B – were part of the inclusion criteria).
2. A pretreatment platelet count of $< 90,000/\text{mm}^3$ is a relative contraindication to starting PEG-IFN therapy.⁷¹

If a pragmatic bleeding risk assessment suggests that a given patient is particularly at risk of developing bleeding in view of the degree of their thrombocytopenia and other comorbidities, eltrombopag therapy may be started to prime the platelet levels to help initiate PEG-IFN therapy.⁹⁷ More studies are needed to validate this indication.

3. CLD patients with thrombocytopenia who need to undergo an invasive procedure may be potential candidates for short 2-week courses of eltrombopag in the peri-procedural period. However, at least one Phase III randomized-controlled trial (the ELEVATE study)⁹⁸ concluded that because of the safety concerns (drug-induced thrombosis, etc) eltrombopag should *not* be used as an alternative to platelet transfusions in CLD patients (with thrombocytopenia) undergoing invasive procedures.

Criteria for discontinuing eltrombopag therapy

Each of the following should be considered an *independent* criterion to discontinue eltrombopag therapy. Eltrombopag therapy should be stopped if:

- after a month of maximum-dose eltrombopag therapy (75 mg/day), the platelet count fails to rise to the target level of $\geq 50,000/\text{mm}^3$
- platelet count rises to $>250,000/\text{mm}^3$; this is the manufacturer's recommendation. Nonetheless, platelet count should be monitored twice weekly (usual is once weekly) and re-initiation of eltrombopag therapy at a low dose of 25 mg once daily be considered if the platelet count subsequently falls to $\leq 100,000/\text{mm}^3$
- serial peripheral blood films show signs of possible bone marrow fibrosis (eg, teardrop cells, nucleated red blood cells, or immature white blood cells) (because eltrombopag may cause bone marrow fibrosis)^{102–104}
- significant hepatotoxicity develops with eltrombopag, which means a rise in alanine aminotransferase levels three times the upper normal limit *and* one of the following:
 - progressively worsening transaminitis
 - transaminitis that persists for ≥ 1 month
 - transaminitis associated with hyperbilirubinemia
 - development of liver-related clinical symptomatology (jaundice, signs of hepatic decompensation, etc).

Dosage

Although the exact indications and dosage of eltrombopag in HCV-related thrombocytopenia have not yet been

unanimously defined, a suggested protocol is outlined following.

- The usual starting dose of eltrombopag in Caucasian people is 50 mg once daily. In patients of East Asian ancestry, a lower dose of 25 mg once daily appears to be equally effective.⁹⁹ Although eltrombopag shows linear pharmacokinetics, a recent randomized open-label Phase II study⁹⁹ showed that rises in platelet counts apparently saturate at doses of 25 mg of eltrombopag in Japanese patients. Any higher doses (37.5 mg once daily in the given study) were associated with higher risk of potentially serious side effects (particularly portal vein thrombosis, ascites, and pleural effusions).⁹⁹
- In patients with Child–Pugh class B CLD, it is suggested that eltrombopag be started at a lower dose of 12.5–25 mg once daily (the more the liver is diseased, the less hepatic eltrombopag metabolism there is and the higher the plasma bioavailability of the drug).⁹⁹
- It usually takes 1–2 weeks for measurable improvements in platelet count to take place. Therefore, as a rule, 2 weeks should be allowed to elapse before the eltrombopag dose is increased (and, thereafter, every time a dose adjustment is made).
- If a platelet count of $<50,000/\text{mm}^3$ persists after 2 weeks of eltrombopag therapy, consideration should be given to increasing the dose by 25 mg/day every 2 weeks to a maximum dose of 75 mg/day.
- The aim should be to achieve and maintain a platelet count of $\geq 50,000/\text{mm}^3$.
- If, after a month of high-dose eltrombopag therapy at 75 mg/day, the platelet count has not risen to the target level of $\geq 50,000/\text{mm}^3$, therapy should probably be discontinued.
- If the platelet count rises to $>150,000/\text{mm}^3$, consideration should be given to reducing the eltrombopag dose by 25 mg and 2 weeks allowed to elapse to determine the effect of this or any subsequent dose reduction. It should be remembered that a platelet count of $\geq 50,000/\text{mm}^3$ be maintained with the minimum effective dose of eltrombopag.

An alternative dosage regimen is intermittent eltrombopag therapy of three cycles of treatment for 6 weeks followed by a 4-week drug holiday. The starting dose remains 50 mg once daily with dose adjustments made to achieve and maintain a platelet count of $\geq 50,000/\text{mm}^3$. One open-label repeat dose study (TRA108057, REPEAT) showed that this intermittent dosing schedule does not lead to loss of response

to eltrombopag therapy.¹⁰⁵ More head-on studies are needed to compare the relative therapeutic efficacies, safety profiles, and cost-effectiveness of continuous versus intermittent dosing schedules.

Monitoring eltrombopag therapy

Full blood count (FBC), peripheral blood film, and liver function tests (LFTs) should be requested at least once per week until the target platelet count of $\geq 50,000/\text{mm}^3$ is maintained for at least one month continuously. Thereafter, the monitoring frequency can be reduced to once every two weeks and later once a month.

The rationale for undertaking FBC is obvious – to monitor platelet levels. Concomitantly requesting peripheral blood film is equally important because eltrombopag has been suggested to cause bone marrow fibrosis in some cases.^{102–104,106,107} After having established the pre-eltrombopag treatment cellular morphology by peripheral blood film, subsequent films are taken to monitor and compare the development of any new or worsening morphological abnormalities (eg, teardrop cells, nucleated red blood cells, or immature white blood cells). As indicated earlier, if there is any suggestion of bone marrow fibrosis, eltrombopag therapy should be discontinued and followed by a formal bone marrow biopsy. Besides the development of cellular morphological abnormalities, failure of platelet count to be maintained after an initial positive response despite increasing the eltrombopag dose to the maximum level is another indication of the possible development of bone marrow fibrosis.

Eltrombopag is potentially hepatotoxic (mild reversible transaminitis can develop) and is known to predispose to portal vein thrombosis even at normal/subnormal platelet counts. In patients with a Child–Pugh score < 5 , eltrombopag therapy can be initiated and dose adjustments made as in any other patient with no hepatic impairment. If the Child–Pugh score is ≥ 5 , eltrombopag is better avoided. However, if the benefits clearly appear to outweigh the risks, it may be started at a low dose of 25 mg once daily and dose adjustments made no earlier than after 3 weeks of active monitoring (normally any dose adjustment is made after a 2-week period). Maximum-dose eltrombopag therapy (75 mg/day) has been found to particularly increase the risk of thromboembolism (portal vein thrombosis and even MI) despite subnormal platelet counts of $\leq 50,000/\text{mm}^3$. Thus, in patients of Caucasian ancestry with a Child–Pugh score of ≥ 5 , a dose of > 50 mg once daily should be avoided/used very cautiously; it is probable that the same holds true for people of other ethnic backgrounds.

As eltrombopag binds highly to plasma proteins, predominantly to albumin, it is predominantly not excreted renally (the main route of excretion is via the feces). Therefore, it is recommended that *no* dose adjustments be made in patients with renal impairment. Nonetheless, patients who already have renal impairment need to be actively monitored for any further derangement (eltrombopag has caused renal tubular toxicity in animal studies).^{90,108}

In patients aged 18 years or younger, eltrombopag therapy is not recommended because of the lack of clinical data.

Patients aged 65 years or older should probably be treated similar to the younger subjects in which no dose adjustments are needed, although more studies are needed in this age group to validate this recommendation.

Drug–drug interactions

Antacids (containing aluminum and magnesium), high-calcium food (eg, dairy products), and multivitamin tablets/mineral supplements chelate, thus significantly reduce the systemic absorption of eltrombopag.⁸⁸ Therefore, it is recommended that eltrombopag be administered at least 4 hours before or after these products are taken. In the unusual scenario of eltrombopag overdose (deranged LFTs and very high platelet levels), oral administration of antacids and dairy products should be expected to limit eltrombopag absorption and cause increased fecal excretion. Since eltrombopag is not renally excreted, hemodialysis is unlikely to be effective in overdose cases.

Eltrombopag increases the therapeutic levels of statins, particularly rosuvastatin. If a statin is required, it is best to switch to low-dose atorvastatin or fluvastatin and actively monitor the patient for the development of any statin-related side effects (eg, myositis). Caution should also be exercised when coadministering eltrombopag and methotrexate. Lopinavir/Ritonavir coadministration with eltrombopag seems to decrease oral absorption and thus the bioavailability of the latter. If coadministration is necessary, platelet counts should be closely monitored so that the eltrombopag dose can be adjusted accordingly.

Safety profile

Higher eltrombopag doses are associated with higher therapeutic efficacy and higher risk of side effects, and vice versa. Although almost 80% of subjects undergoing eltrombopag therapy develop one or more side effects, the most commonly reported side effects in the published literature (headache [13% – the commonest side effect], cataract, dry eyes, dry mouth, pharyngitis, abdominal pain, nausea, vomiting,

diarrhea, constipation, insomnia, paresthesias, arthralgia, myalgia, peripheral edema) were of insufficient severity to require discontinuation of the drug.¹⁰⁹ Potentially serious side effects of eltrombopag therapy that may require discontinuation of the drug include thromboembolism (portal vein thrombosis, MI, cerebrovascular accident, deep vein thrombosis, pulmonary embolism), rebound thrombocytopenia after discontinuation of eltrombopag therapy with secondary increased risk of bleeding, hepatotoxicity, and bone marrow fibrosis.

Eltrombopag has been found to cause thromboembolism, especially portal vein thrombosis at normal or even subnormal platelet levels.^{98,109–114} Therefore, eltrombopag should only be used when the benefits of doing so clearly outweigh the risks in high-risk patient groups such as patients who already have evidence of hepatic impairment (Child–Pugh score ≥ 5) and patients who have known risk factors for thromboembolism such as deficiencies in Factor V Leiden, AT-III, protein C, and protein S or antiphospholipid syndrome. Likewise, patients with poor mobility (due to advanced senility, post-surgery/trauma, morbid obesity, etc), cancer patients, and patients on an oral contraceptive pill or hormone replacement therapy are also high risk for thromboembolism.

In high-risk patients, eltrombopag should be used in a dose that is just sufficient to achieve and maintain the target platelet count of $\geq 50,000/\text{mm}^3$. Ideally, platelet count should not be allowed to rise above $100,000/\text{mm}^3$ in high-risk patients.

The reason why eltrombopag predisposes to thromboembolism despite normal or subnormal platelet counts is not yet clear. Eltrombopag therapy itself probably does not produce any ill effects on platelet function as measured by platelet activation and aggregation, although more studies are needed to validate this observation.^{109,110} It has been postulated that both in HCV-related thrombocytopenia and CITP cases (regardless of whether treated with eltrombopag), the platelets become more “sticky,” thus may aggregate and form a thrombus, despite low counts.^{111,112} A rapid increase in platelet count when eltrombopag is used at high doses of 75 mg, especially in patients with liver impairment, probably also predisposes to TEEs. Additionally, the increased incidence of endothelial damage seen in liver disease may also be a contributory factor. These postulations may explain why many patients with severe thrombocytopenia never develop any significant bleeding.¹¹⁶ There are conflicting reports in the literature regarding whether eltrombopag further increases the physiological stickiness of platelets. While several case reports incriminated eltrombopag in

increased reactivity of platelets with consequent increased propensity to aggregation and thrombus formation,¹¹³ recently, some small in vitro and in vivo studies have refuted any such link.^{114,115,117, 118} The first in vivo report on TPO-RAs on platelet reactivity only studied 20 patients.¹¹⁴ Therefore, more studies on larger cohorts of patients are needed to clarify this controversy that may have important implications on the future acceptability and use of this drug.

In the majority of patients, the platelet count falls to pretreatment levels within 2 weeks of discontinuing eltrombopag therapy, thus predisposing them to bleeding. To avoid this risk, adjunct eltrombopag therapy may need to be continued for several weeks in HCV-positive cases undergoing antiviral therapy (although the exact duration of eltrombopag therapy will vary from case to case; further, data on the continued use of eltrombopag for >6 months is very limited).^{101, 119–121} Platelet count should be monitored weekly for at least 1 month following discontinuation of eltrombopag therapy. A recent study has suggested that the observation that platelet count returns to baseline within 2 weeks of treatment discontinuation is based on studies done in CITP patients.^{96, 122} In contrast, in CLD patients with thrombocytopenia, platelet counts have been shown to continue to increase in the week following treatment discontinuation and thereafter fall rather gradually.⁹⁹ The exact underlying reason for this important difference is not yet clear; nonetheless, it is argued that since eltrombopag is primarily metabolized in the liver, in CLD patients, the plasma eltrombopag concentrations during treatment and for a few days post-treatment are generally higher than in CITP patients.^{90,123} More studies are needed to demonstrate the probable reduced risk of bleeding in the immediate post-treatment period in CLD patients compared with CITP patients.

Different studies have suggested that eltrombopag causes bone marrow fibrosis.^{102,103} Although the exact mechanism has not yet been established, it is thought to involve the release of transforming growth factor beta from eltrombopag-activated megakaryocytes, which in turn causes a reversible increase in reticulin deposition.^{124, 125} This finding is backed by similar observations made in animal studies in which use of second-generation TPO-RAs was shown to cause extensive bone marrow fibrosis with secondary extramedullary hematopoiesis (comparable to human myelofibrosis).^{102–104} Because of the relative paucity of data on human subjects, more long-term exposure studies are needed to explore this potentially dangerous complication in humans¹²⁶ (a 2-year longitudinal bone marrow study [NCT01098487], which includes baseline

and repeated bone marrow examinations is currently underway).¹⁰⁰ As mentioned, if serial peripheral blood films suggest new or worsening cellular morphology indicating possible development of bone marrow fibrosis, eltrombopag therapy should be stopped. Clinically, if platelet levels fail to improve or be maintained despite optimal eltrombopag therapy in the recommended dosing range, bone marrow fibrosis/impairment should be suspected.

An association between autoimmune diseases and risk of development of hematologic malignancies is well established in the medical literature.¹²⁷ Autoimmune thrombocytopenia is known to be the first manifestation of a hematologic malignancy in many patients and may actually precede its onset by several years. Stimulation of hematopoietic stem cells by eltrombopag may thus theoretically increase the risk of development of hematologic malignancy. Both preclinical studies^{128,129} and the EXTEND study¹⁰⁰ have shown that eltrombopag does not promote proliferation of malignant cells, thus does not increase the risk of hematologic malignancy.

Despite some conflicting reviews in the literature, it is the opinion of the authors of the present review that pregnancy be regarded as an absolute contraindication for IFN, RBV, and eltrombopag therapies. Any HCV-infected woman of child-bearing age who wants to be treated for HCV infection must observe strict contraceptive measures for the entire duration of the therapy plus at least 6 months thereafter. This is because all three of these agents have repeatedly been shown to have teratogenic and/or embryocidal effects in animal studies and the potential risks in humans are unknown at this stage.^{130,131} Likewise, lactating mothers should not be offered any of these agents because, while the risk in human subjects is unknown, it is known from animal studies that all three agents are likely to be secreted in breast milk.

Eltrombopag does not appear to prolong QT interval in healthy subjects in doses between 50–150 mg in comparison to placebo.¹⁰⁸

Cost-effectiveness

In the UK, one 50 mg tablet of eltrombopag costs £55, which makes a 1-month course of 50 mg once daily cost £1650 (although, due to negotiated procurement discounts the precise cost may vary). Limited data are available on the cost-effectiveness of this novel agent in the treatment of HCV-related thrombocytopenia; nonetheless, a recent National Institute of Health and Clinical Excellence UK technology appraisal on the use of eltrombopag in CITP patients concluded that eltrombopag is not a cost-effective use of National

Health Service resources.¹³² Based on manufacturer's deterministic sensitivity analyses for the acquisition cost of eltrombopag (£50–£60 per 50 mg), it was reported that the incremental cost-effectiveness ratios (ICERs) ranged from £77,496 per quality-adjusted life year (QALY) gained for splenectomized people to £90,471 per QALY gained for non-splenectomized people. The highest ICER reported was £99,441 per QALY gained for the non-splenectomized population (based on the acquisition cost of £60 per 50 mg tablet). The lowest ICER reported was £69,301 per QALY gained for the splenectomized population (based on the acquisition cost of £50 per 50 mg tablet). In a subsequent publication, Boyers et al reported that substantial reductions in the cost of eltrombopag are needed before the incremental cost per QALY drops to the recommended threshold of £30,000 per QALY gained.¹³³

Future considerations

Good-quality randomized-controlled trials need to be undertaken regarding the role of eltrombopag specifically in the treatment of HCV-related thrombocytopenia. Further, more studies on larger cohorts of patients are needed to clarify whether or not eltrombopag causes increased in vivo platelet reactivity (stickiness), thus predisposes to thromboembolism. Studies are also required that directly compare eltrombopag with romiplostim to determine their relative therapeutic efficacies, safety profiles, and cost-effectiveness. Indirect comparison of the data from the RAISE trial⁹⁵ suggests that eltrombopag is probably less efficacious than romiplostim (the latter has recently been approved by the National Institute for Health and Clinical Excellence in the UK for use in CITP patients). In addition, more head-on studies are needed to compare the relative therapeutic efficacies, safety profiles, and cost-effectiveness of continuous versus intermittent eltrombopag dosing schedules. Finally, more long-term exposure studies and pharmacovigilance activities are necessary to specifically explore the safety concerns of second-generation thrombopoietic growth factors (eltrombopag, romiplostim) on bone marrow function in human subjects, hepatotoxicity, TEEs, recurrence of thrombocytopenia following cessation of eltrombopag therapy, potential for increase in hematologic malignancies, cataracts/phototoxicity, renal tubular toxicity, and endosteal hyperostosis.

Conclusion

Although more studies are needed to validate the true indications, dosage schedule, therapeutic efficacy, and safety profile of eltrombopag adjunct therapy in HCV-related

thrombocytopenia, from the authors' knowledge of the use of this novel agent in CITP, it appears that it is an efficacious treatment modality for the short-term amelioration of thrombocytopenia.¹³⁴ There are some relatively serious safety concerns related to the use of this drug in CLD patients, particularly treatment-related thrombosis. It does not appear to be a safe alternative to repeated platelet transfusions in CLD patients undergoing an invasive procedure. Nonetheless, if a last-resort decision to use eltrombopag in the periprocedural period is being made, this drug should normally be used for short-term periods of ~2 weeks and at the lowest possible effective dose (usually 12.5–50 mg once daily in CLD patients). At the time of writing this article, eltrombopag does not seem cost-effective.¹³⁵

Disclosure

The authors declare no conflicts of interest in this work.

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