Considerations in the Management of HCV-related Thrombocytopenia with Eltrombopag

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1 Introduction

Hepatitis C virus (HCV) infection is estimated to have chronically infected 160 million individuals worldwide (Lavanchy, 2011). HCV is known to cause thrombocytopenia even in the absence of overt hepatic disease (Pyrsopoulos & Reddy, 2001; Cacoub et al., 2000) and is considered a surrogate marker for the severity of liver disease (Afdhal et al., 2008). It is sometimes the only manifestation of viral hepatitis. Chiao et al. (2009) suggested that HCV infection is associated with an increased risk of developing chronic immune thrombocytopenic purpura (CITP) (HR, 1.8; 95% CI, 1.4 – 2.3). Similarly, Pockros et al. (2002) retrospectively estimated that the prevalence of CITP among their HCV patients was much greater than would be expected by chance (P < .00001). Conversely, many cross-sectional studies have reported positive HCV serology (up to 20%) in patients with a clinical diagnosis of CITP (Garcia-Suarez et al., 2000; Sakuraya et al., 2002). The documented severity of thrombocytopenia in different studies has been highly variable; may range from mild to severe. Thrombocytopenia is a well known relative contraindication for the initiation of antiviral therapy in HCV-infected patients. Thrombocytopenia may also result in the postponement of many invasive procedures that CLD patients may need to undergo like percutaneous, transjugular or laparoscopic liver biopsy, paracentesis, thoracentesis, radiofrequency ablation (RFA) or partial hepatectomy for hepatocellular carcinoma (HCC). Latter group of patients may also need to undergo splenectomy especially if the platelet counts are < 50,000/µL. Mild (> 75,000/µL – < 150,000/µL) to moderate (50,000/µL – 75,000/µL) thrombocytopenia is only rarely associated with any bleeding complications (Afdhal et al., 2008). Doing invasive procedures in the background of severe thrombocytopenia (< 50,000/µL) however may be associated with significant morbidity necessitating repeated platelet transfusions in the peri-operative period (Giannini et al., 2006; McCullough, 2000; Tripodi & Mannucci, 2007). Platelet transfusions are generally effective for only a few hours; moreover, these may be associated with multiple potential complications like febrile non-hemolytic & allergic reactions, platelet refractoriness (due to HLA alloimmunization), iron overload (with chronic repeated transfusions), need for hospitalization, risk of infection and cost (McCullough, 2000; Perrotta & Snyder, 2001). This explains the need & rationality to have an alternative therapeutic option to help raise the platelet counts when needed. Different therapeutic strategies have been suggested & tried to treat HCV-related thrombocytopenia in different studies with variable success rates (generally disappointing) (Nurden et al., 2009). Recent introduction of 2nd generation thrombopoietin-receptor (TPO-R) agonists has opened up a novel way to treat thrombocytopenia. FDA approved Eltrombopag and Romiplostim in CITP patients’ refractory to at least one standard treatment in 2008.

2 Cause-effect Relationship between HCV Infection & Thrombocytopenia

In areas of high HCV seroprevalence, it is generally recommended that if a patient presents with thrombocytopenia & has one or more risk factors for HCV present, he/ she should be screened for the virus (Rajan et al., 2005; Stasi, 2009). Important risk factors that should prompt checking for HCV status include needle stick injury or mucosal exposure to HCV-positive blood, I/V drug abusers, multiple blood transfusions, haemodialysis, current sexual partners of HCV-infected persons or persons having multiple sexual partners, children born to HCV-infected mothers & unexplained abnormal aminotransferase levels. Multiple studies have demonstrated significant improvements in platelet counts following successful
treatment of HCV infection suggesting the latter being a possible cause of thrombocytopenia (Iga et al., 2005; Zhang et al., 2003). In fact, several studies have suggested that thrombocytopenia is found in as much as 76% cases of cirrhosis of liver (Bashour et al., 2000; Qamar et al., 2009). The severity of thrombocytopenia is generally directly proportional to the severity of the chronic liver disease (CLD) (Peck-Radosavljevic, 2000; Sallah & Bobzien, 1999). Although thrombocytopenia is generally less severe in HCV-infected patients compared to CITP patients, the former are more prone to major bleeding episodes due to liver disease associated coagulopathy & portal hypertension. Interestingly, a recent study (Giannini et al., 2010) suggested that it is thrombocytopenia rather than coagulopathy that is the major determinant of bleeding risk in patients with CLD. The same study estimated the bleeding incidence to be 31% in patients with platelet count < 75,000/mm$^3$. WHO classifies bleeding into grade 1 (petechiae), grade 2 (mild blood loss), grade 3 (gross blood loss) & grade 4 (debilitating/life threatening blood loss) (Fogarty et al., 2011).

Possible causes for HCV-related thrombocytopenia include:

1. **Decreased platelet production:** This in turn could be due to decreased hepatic production of thrombopoietin (a glycoprotein that promotes megakaryopoiesis) (Adinolfi et al., 2001; Peck-Radosavljevic et al., 1998) & direct suppressant effect of HCV on bone marrow (Ballard et al., 1989; Bordin et al., 1995).

2. **Increased peripheral destruction of platelets:** This in turn could be due to immune-mediated peripheral platelets destruction and hypersplenism leading to increased splenic platelet sequestration (McCormick & Murphy, 2000; Weksler, 2007). Since, HCV is known to cause thrombocytopenia even in well-compensated cases (in the absence of portal hypertension & hypersplenism) (Sakuraya et al., 2002; Zhang et al., 2003) and thrombocytopenia has been shown to persist after portal decompression in established cases of hypersplenism (decompensated cirrhotics) (Jabbour et al., 1998), it appears logical to believe that probably immune-mediated destruction of platelets is more dominant a mechanism of thrombocytopenia than hypersplenism. HCV binding to platelet membrane with consequent binding of anti-HCV antibody and phagocytosis of platelets (called “innocent bystander” phagocytosis) (Hamaia et al., 2001), and an HCV protein mimicking an epitope on platelet surface (called GPIIIa) triggering the production of anti-platelet antibodies are the two most frequently postulated immune mechanisms explaining increased peripheral platelet destruction in HCV-infected cases (Bordin et al., 1995; Hamaia et al., 2001; Nagamine et al., 1996; Pockros et al., 2002).

3. **Iatrogenic:** Interferon (IFN) therapy is also known to suppress bone marrow with consequent 10 – 50% fall in the platelet count (Peck-Radosavljevic et al., 1998). Pegylated interferon/ ribavirin (PEG-IFN/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 (Fried et al., 2002) suggesting that coomitant ribavirin therapy probably has some protective effect (causes reactive thrombocytosis) (Peck-Radosavljevic et al., 1998). In one study, PEG-IFN therapy-induced thrombocytopenia lead to dose reductions in 19% cases and discontinuation in 2% cases (Sulkowski et al., 2005). In cirrhotic patients, the incidence of treatment induced thrombocytopenia is generally higher than in non-cirrhotics (Bashour et al., 2000).
Interestingly & paradoxically, advanced liver disease patients, such as cirrhotics, are not only predisposed to bleeding (secondary to thrombocytopenia & coagulopathy), but also to thromboembolic events (TEEs), especially portal/ splenic vein thrombosis. Reduced portal vein flow & possible presence of intra-abdominal cancer are two pertinent predisposing factors for the development of TEEs in such patients (Amitrano et al., 2007; Lisman et al., 2010; Tripodi et al., 2010). Performance of an invasive procedure in cirrhotics & hepatocellular carcinoma patients is also considered an independent risk factor for the development of portal vein thrombosis (incidence estimated to be up to 35%) (De Stefano et al., 2010; Kulik et al., 2008). It appears that patients who undergo an invasive procedure involving splanchnic circulation (e.g. variceal banding, radiofrequency ablation or transarterial chemoembolization) are particularly vulnerable to develop portal/ splenic vein thrombosis (Afdhal et al., 2012).

3 Pathophysiology of Thrombopoietin

Thrombopoietin (TPO), a glycoprotein primarily produced by hepatocytes, is the major regulator of both megakaryopoiesis and platelet production in human body. It is the key endogenous ligand for thrombopoietin receptor (TPO-R) found on the surface of megakaryocytes, and megakaryocytic precursors (Kuter & Begley, 2002; Kaushansky & Drachman; 2002). TPO binding to its receptor activates the Janus Kinase/Signal Transducer and Activator of Transcription (JAK-STAT) pathway ultimately leading to the release of platelets in the circulation (Ezumi et al., 1995; Rojnuckarin et al., 1999; Drachman et al., 1999). 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 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. Studies have shown that the grade of liver fibrosis, the severity of TPO deficiency and the incidence of thrombocytopenia are all positively correlated (Adinolfi et al., 2001). Correction of TPO deficiency by ‘liver transplantation’ has been shown to improve megakaryopoiesis and thus circulating platelet levels (Goulis et al., 1999; Peck-Radosavljevic et al., 2000).

4 Different Therapeutic Strategies to Treat HCV-related Thrombocytopenia

Since successful treatment of HCV infection has clearly been shown to improve the platelet counts (Pockros et al., 2002; Rajan & Liebman, 2001), the therapeutic protocol for managing HCV-related thrombocytopenia ought to differ from that of primary (idiopathic) thrombocytopenic purpura. The therapeutic strategies employed in different studies to treat HCV-related thrombocytopenia include a reduction in the dose of IFN (Rajan & Liebman, 2001), addition of a new drug like oral steroids (Hernandez et al., 1998; Ramos-Casals et al, 2003; Sakuraya et al., 2002; Zhang et al., 2003), intravenous immunoglobulin (IVIG) (Garcia-Suarez et al., 2000), or anti-RhD Ig (Rajan et al., 2005), resorting to an invasive procedure like partial splenic embolization (Giannini & Savarino, 2008), splenectomy (Sakuraya et al., 2002; Zhang et al., 2003), or transjugular intrahepatic portosystemic stent shunt (TIPSS) placement. Although steroids are commonly used in CITP patients, their use in HCV-infected patients has shown to cause statistically-significant rises in transaminase levels & HCV viral loads, and worsening of liver damage (Rajan et al.,
They have even shown to cause hyperbilirubinemia and development of overt jaundice (rarely). 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 counts. Based on this it is recommended that all patients who are suspected to suffer from ‘CITP’ be investigated for Hep-C serology. This recommendation will hopefully prevent the potential adverse effect of prolonged corticosteroid usage on the underlying infection, if present. Splenic artery embolization & splenectomy are often effective in increasing the platelet levels in patients with portal hypertension regardless of Hep-C serology status (Sakuraya et al., 2002; Zhang et al., 2003). These however may be associated with such complications as splenic abscesses and portal vein thrombosis. Portal decompression with TIPSS placement may or may not improve platelet levels because of multifactorial pathogenesis of the latter (Jabbour et al., 1998; Wong, 2006). The American Society of Clinical Oncology recommends platelet transfusions for cancer patients with platelet counts of 10,000/µL – 20,000/µL (Schiffer et al., 2001). American Society of Hematology (ASH) suggests that in ITP patients without other risk factors, platelet levels of 30,000 – 50,000/µL are required to preclude most serious bleeding (intracerebral or major gastrointestinal) complications (George et al., 1996). 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/µL may be considered appropriate; in complicated thrombocytopenic patients (e.g. those with fever, infection, splenomegaly etc), a higher cut-off value such as < 50,000/µL should be regarded as appropriate (Rebulla, 2000; Rinder et al., 1999) (platelet levels of ≥ 50,000/µL are often considered ‘safe’ for ‘most’ invasive procedures) (George, 2004; Provan et al., 2010).

The most practical strategy in treating HCV-related thrombocytopenia is based on the hypothesis that eradication of HCV infection should result in remission of thrombocytopenia. Pre-treatment platelet count of < 90,000/mm³ is a relative contraindication to start PEG-IFN therapy (Calvaruso & Craxi, 2011). If pre-treatment platelet level is above this cut-off value, & 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 platelet count are < 30 × 10⁹/L, or to discontinue it if < 20 × 10⁹/L (Danish et al., 2008; Sherman et al., 2007). Reductions in the dosage schedule of PEG-IFN can compromise the success of the therapy. To help maintain optimal dosage schedule, adjunct eltrombopag (or romiplostim) may be considered to counteract thrombocytopenia in a sustained manner (Danish et al., 2008, 2010). Eltrombopag is already recommended in CITP cases in two scenarios:

1. Post-splenectomy CITP patients who are refractory to other drug therapies (e.g. corticosteroids, immunoglobulins).

2. Patients in whom splenectomy is contraindicated and other medical agents have failed to correct thrombocytopenia.

Recently, eltrombopag has been used successfully in 2 cases of persistently thrombocytopenic, platelet transfusions-dependent patients following stem-cell transplantations (one allogeneic & one autologous) (Reid, 2012). In both cases, the patients became platelet transfusion independent with platelets counts ~30,000/µL & ~10,000/µL respectively within ~2 weeks of starting eltrombopag treatment. It is pertinent to mention here that the usefulness of repeated platelet transfusions is limited by their short duration of efficacy, risk of transfusion-related reactions & almost 50% incidence of alloimmunization (development of antiplatelet antibodies leading to refractory thrombocytopenia non-responsive to repeat
platelet transfusions) (Poordad, 2007; Slichter, 2007; Trotter, 2006;). It thus appears that the therapeutic indications of eltrombopag may expand in the coming years (provided the drug proves relatively safe in human subjects, & the cost is not inhibiting).

5 **Historical Note: Use of 1st-generation Thrombopoietic Growth Factors in Treating HCV-related Thrombocytopenia**

Historically, multiple clinical trials (de Sauvage, 1994; Kaushansky, 1994a, 1994b; Wendling, 1994), showed improvements in platelet counts with 1st-generation thrombopoietic growth factors (recombinant human thrombopoietin [TPO] & pegylated recombinant human megakaryocyte growth and development factor [PEG-rHuMGDF]). However, their use was unexpectedly forsaken in 1998 when some patients paradoxically developed thrombocytopenia secondary to PEG-rHuMGDF use (Basser et al., 2002; Bartley et al., 1994; Harker et al., 2000; Li et al., 2001;). 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 nonimmunogenic 2nd-generation TPO-receptor agonists - Romiplostim [AMG-531, Nplate(R)] & Eltrombopag [SB-497115, Promacta(R), Revolade(R)] (Panzer, 2009).

Recently, the manufacturer of eltrombopag conducted an indirect comparison between eltrombopag and romiplostim in CITP. 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 (splenectomised or non-splenectomised). Similarly, no significant differences in the incidence of bleeding adverse events (grade 2 or higher) were noted.

6 **Role of Eltrombopag (2nd-generation Thrombopoietic Growth Factor) in Treating HCV-related Thrombocytopenia**

6.1 **Aim of Treatment**

The ultimate aim of treating thrombocytopenia in HCV-positive cases is not to normalize the platelet counts (Vizcaíno et al., 2009) but to maintain them above the level of haemorrhagic risk (> 50,000/µl) thus conferring the advantage of possible avoidance of interferon dose reductions or interruptions.

6.2 **Mechanism of Action**

Eltrombopag is a thrombopoietin-receptor agonist (TPO-RA) (Erickson-Miller et al., 2005; Juan et al., 2004; Kalota et al., 2004). The ligand-receptor binding activates JAK2/STAT signalling pathways inducing increased proliferation and differentiation of human bone marrow progenitor cells into megakaryocytes. The net effect is an increase in the circulating platelets count (Erickson-Miller, 2004). It appears that eltrombopag binds the TPO receptor at a distance from the binding site for endogenous TPO and appears to initiate signal transduction by a different mechanism (Erickson-Miller, 2009). The two thus may have an additive (**& not competitive**) effect on platelet production. Endogenous TPO appears to be 7-9 times more potent than eltrombopag.
6.3 Pharmacokinetics

It appears that the pharmacokinetics of Eltrombopag (peak concentration 2 – 6 h after oral administration; average $T_{1/2} > 12$ hours) is linear and therefore it produces a dose-dependent increase in platelet proliferation and differentiation (higher doses are more effective & less safe!) (Bussel et al., 2007; Erickson-Miller et al., 2005; Jenkins et al., 2007; Julian et al., 2007; Luengo, 2004; Sellers et al., 2004). Eltrombopag should be taken at least four hours before or after antacids, dairy products & multi-vitamin tablets/mineral supplements as these products chelate & thus significantly reduce the systemic absorption of eltrombopag (Williams et al., 2009). Although the absolute oral bioavailability of eltrombopag in human subjects has not been well established, it is estimated to be at least 52%. 99.9% of absorbed eltrombopag circulates bound to plasma proteins, predominantly albumin. Circulating eltrombopag undergoes extensive hepatic metabolism through cleavage, oxidation & conjugation with glucuronic acid, glutathione or cysteine. Since individual UGT enzymes only show a limited contribution in the glucuronidation of eltrombopag, significant drug interactions involving glucuronidation are not anticipated with this drug. Also, eltrombopag doesn’t appear to inhibit or induce CYP enzymes in both in vitro & in vivo studies. This implies that no clinically significant interactions should be expected when eltrombopag and CYP inducers or inhibitors are co-administered. Since eltrombopag is primarily metabolized in the liver, higher plasma eltrombopag concentrations are reported in HCV infected patients compared to CITP patients or healthy volunteers (Bauman et al., 2011). Inter-ethnic 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 to Caucasians who usually require double this dose) (Gibiansky et al., 2011). The underlying mechanism accounting for the observed inter-ethnic 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 to the general Caucasian population) (Shida et al., 2011). Since the clearance of eltrombopag increases with increase in body weight (Gibiansky et al., 2011), heavy subjects need higher doses to produce an identical therapeutic effect. Another possible explanation is the known inter-ethnic differences (Mizutani, 2003; Zhang et al., 2007) in the levels of activities of different drug metabolising enzymes involved in eltrombopag metabolism (e.g. cytochrome P450 (CYP) 1A2, CYP2C8, uridine diphosphate-glucuronosyltransferase (UGT) 1A1, and UGT1A3 etc) (Shida et al., 2011). The predominant route of eltrombopag excretion is via faeces (59%) followed by urine (31%). Via the latter, only metabolites (& not the parent drug) are found to be excreted.

6.4 Evidence of Therapeutic Efficacy

The evidence of effectiveness of eltrombopag primarily comes from two phase-III, randomised, double-blind, placebo-controlled trials done on CITP patients.

In a recent phase-III, randomised, double-blind, placebo-controlled study (Cheng et al., 2011), 197 CITP patients were randomised 2:1 (eltrombopag [n = 135] to placebo [n = 62]). Median platelet counts at baseline were 16,000/µL 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 (106 i.e. 79% patients) in the eltrombopag group. 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 8.2, 99% CI 3.59 – 18.73; $p < 0.0001$). A platelet count between 50,000 – 400,000/µL 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 re-
sulted in 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, randomised, double-blind, placebo-controlled study (Bussel et al., 2009), CITP patients having platelet counts of < 30,000/µL were given eltrombopag in a dose of 50mg once-daily (n = 76) or placebo (n = 38) for up to 6 weeks. The target was to achieve platelet counts of ≥ 50,000/µL at day 43. Whereas, only 16% placebo-treated patients achieved the target platelet count, the same was achieved in 59% of eltrombopag-treated patients (odds ratio [OR] 9.61 [95% CI 3.31 – 27.86]; p < 0.0001). Also eltrombopag-treated patients showed less instances of bleeding complications at any given time during the study compared to the placebo group (OR 0.49 [95% CI 0.26 – 0.89]; p = 0.021).

In a phase 2 study (McHutchison et al., 2007), whereas only 6% of HCV-related cirrhotics in the placebo group completed the 12 weeks antiviral course, the same was completed by 36%, 53%, and 65% of patients receiving 30 mg, 50 mg, and 75 mg of eltrombopag respectively. Moreover, 75 to 95% of patients in the eltrombopag groups achieved the primary end point (a platelet count 100,000/mm³ at week 4) in a dose-dependent manner. During this study, 7 patients reported serious adverse effects, namely:

- Ascites (in the group receiving 30 mg of eltrombopag). This led to withdrawal of eltrombopag in 3 patients. Ascites resolved subsequently.
- Retinal exudates (in the group receiving 75 mg of eltrombopag). This led to withdrawal of eltrombopag in 1 patient. Retinal exudates failed to resolve subsequently & investigators were of the view that these were unrelated to eltrombopag therapy.

In a recent double-blind, randomized, placebo-controlled, phase 3 clinical trial conducted in 13 countries (ELEVATE study), 292 patients with chronic liver disease (CLD) due to variable causes & with associated thrombocytopenia (platelet count < 50,000/mm³) 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) (Afdhal et al., 2012). Avoidance of platelet transfusion before, during & up to 7 days after the procedure was set as the primary end point. The results showed that primary end point was successfully achieved in 72 % (104 of 145) patients in eltrombopag group compared to only 19% (28 of 147) in the placebo group (p < 0.001). Bleeding episodes of WHO grade 2 or higher were reported in 17% & 23% of patients, respectively. Importantly, this study showed the development of portal venous thrombosis in 6 patients receiving eltrombopag, compared to only 1 in the placebo group. In total 10 thromboembolic events (TEEs) were recorded in 8 patients – 7 events in the eltrombopag group & 3 events in the placebo group (odds ratio with eltrombopag, 3.04; 95% CI, 0.62 to 14.82). All events occurred 1 – 38 days after cessating eltrombopag or placebo therapy. 9 out of 10 TEEs involved symptomatic portal or splenic vein thrombosis – all occurring in the eltrombopag group; the 1 TEE that occurred in the placebo group was MI. All affected patients in the eltrombopag group except 1, developed TEE at platelet levels of ≥ 200,000/mm³. The post hoc analysis confirmed an association between platelet levels of ≥ 200,000/mm³ & increased risk of portal venous thrombosis. The study concluded that till the time more data is being made available with further studies on the safety profile of eltrombopag, this 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 (Kawaguchi), 12 CLD patients with platelet counts < 50,000/µL received 12.5 mg eltrombopag once daily for 2 weeks. After evaluating the safety of the drug, in the 2nd 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/µL (95 % CI 8,200 – 41,400), 54,000/µL (95 % CI 28,200 – 79,800), and 60,000/µL (95 % CI 29,300 – 90,700) in the 12.5, 25, & 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 in a dose of 25 mg daily is effective in alleviating thrombocytopenia in CLD patients.

The safety and efficacy of long-term use of eltrombopag (299 CITP patients treated for up to 3 years) has been tested recently in the interim analysis (Mansoor et al., 2012) of an ongoing, global, multicenter, open-label EXTEND study (Saleh et al., 2010). The results showed that a platelet level of ≥ 50,000/µL was achieved at least once in both splenectomised and non-splenectomised patients (80% & 88% respectively for a median of 73 of 104 and 109 of 156 cumulative study weeks, respectively). ≥70% of patients who previously failed to respond or relapsed after either rituximab therapy or splenectomy achieved at least once the target platelet level of ≥ 50,000/µL. The same target was achieved for > 50% of study visits in almost 50% of patients who had been treated with ≥ 4 prior ITP treatments. Bleeding symptoms (WHO grades 1 – 4) decreased from a baseline of 56% to 20% at 2 years & 11% at 3 years reflecting the inverse relationship between platelets and bleeding severity in CITP patients (Provan et al., 2010). 13% patients experienced ≥ 1 adverse events leading to study withdrawal. 6 of these patients withdrew due to hepatotoxicity. It was the conclusion of this interim analysis that long-term treatment with eltrombopag is effective in achieving & maintaining target platelet levels; also, this drug is well-tolerated and generally safe.

6.5 Starting criteria of eltrombopag therapy

1. Thrombocytopenia is the underlying reason in almost 6% cases of PEG-IFN dose reductions or withdrawals (Fried et al., 2002). In an HCV-positive patient on antiviral therapy, consider initiating eltrombopag therapy if platelet count falls to < 50,000/µl AND Child-Pugh score is < 5 AND detailed history & examination suggests a realistic risk of bleeding. If Child-Pugh score is ≥ 5, it is better to avoid eltrombopag or used only when benefits clearly outweigh the risks with active monitoring (in the recent phase-II Japanese study (Kawaguchi), Child–Pugh score of 9 or less i.e. Child–Pugh classes A & B were part of the inclusion criteria).

2. Pre-treatment platelet count of < 90,000/mm³ is a relative contraindication to start PEG-IFN therapy (Calvaruso et al., 2012). If a pragmatic bleeding risk assessment suggests that a given patient is particularly at risk of developing bleeding in view of his/ her degree of thrombocytopenia & other comorbidities, eltrombopag therapy may be started to prime the platelet levels to help initiate PEG-IFN therapy (McHutchison et al., 2007). 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 weeks courses of eltrombopag in the peri-procedural period. At least one phase 3, randomized-controlled trial (ELEVATE study) however 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.

6.6 Stopping Criteria of Eltrombopag Therapy

Each of the following should be considered an independent criterion to stop eltrombopag therapy:
1. If after a month of maximum-dose eltrombopag therapy (75 mg/day), the platelet count fails to rise to the target level of \( \geq 50,000/\mu l \).

2. The manufacturer recommends that eltrombopag therapy should be stopped if platelet count rises to \( > 250,000/\mu l \). Nonetheless, platelet count should be monitored twice weekly (usual once weekly) and reinitiating eltrombopag therapy in a low dose of 25 mg once daily be considered if platelet count subsequently falls to \( \leq 100,000/\mu l \).

3. If serial peripheral blood films show signs of possible bone marrow fibrosis (e.g. teardrop cells, nu-cleated RBC’s or immature WBC’s). Eltrombopag is suggested to cause bone marrow fibrosis.

4. If significant hepatotoxicity develops with eltrombopag, which means a rise in ALT levels three times the upper normal limit AND one of the following:
   a) Progressively worsening transaminitis.
   b) Transaminitis that persists for \( \geq 1 \) month.
   c) Transaminitis associated with hyperbilirubinemia.
   d) Development of liver-related clinical symptomatology (jaundice; signs of hepatic decompensation etc).

6.7 Dose of Eltrombopag

Although the exact indications and dosage of eltrombopag in HCV-related thrombocytopenia are not yet unanimously defined, a suggested protocol is given below:

- The usual starting dose of eltrombopag in Caucasian population is 50 mg once daily. In patients of East Asian ancestry, a lower dose of 25 mg once daily appears to be equally effective (Kawaguchi) although eltrombopag shows linear pharmacokinetics, a recent randomized, open-label, phase-II study 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 & pleural effusions).

- In patients with Child–Pugh class B also, it is suggested to start eltrombopag at a lower dose of 12.5 – 25 mg once daily (the more the liver is diseased, the less is the hepatic eltrombopag me-tabolism & higher the plasma bioavailability).

- It usually takes 1 – 2 weeks for measurable improvements in platelets counts to take place. Therefore, as a rule, wait for two weeks before increasing eltrombopag dose (and thereafter every time a dose adjustment is made).

- If a platelet count of \(< 50,000/\mu l \) persists after two weeks of eltrombopag therapy, consider increasing the dose by 25 mg/day every two weeks to a maximum dose of 75 mg/day.

- Aim to achieve and maintain a platelet count of \( \geq 50,000/\mu l \).

- If after a month of high dose eltrombopag therapy at 75 mg/day, the platelet count fails to rise to the target level of \( \geq 50,000/\mu l \), probably it is best to stop this therapy.

- If platelet count rises to \( > 150,000/\mu l \), consider reducing the eltrombopag dose by 25 mg and wait for two weeks to see the effect of this or any subsequent dose reductions. Remember that a
platelet count of $\geq 50,000/\mu l$ should be maintained with the minimum effective dose of eltrombopag.

An alternative dosage regimen is ‘intermittent’ eltrombopag therapy for 6 weeks followed by a 4 weeks drug holiday $\times$ 3 cycles. The starting dose remains 50 mg once daily with dose adjustments made to achieve & maintain a platelet count of $\geq 50,000/\mu l$. One open label, repeat (TRA108057, REPEAT) dose study showed that this intermittent dosing schedule does not lead to loss of response to eltrombopag therapy. More head-on studies are needed to compare the relative therapeutic efficacies, safety profiles and cost-effectiveness of the ‘continuous’ vs. ‘intermittent’ dosing schedules.

### 6.8 Monitoring Eltrombopag therapy

Full blood count (FBC), peripheral blood film and liver function tests (LFT’s) should be requested at least once weekly till the target platelet count of $\geq 50,000/\mu l$ 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 doing FBC is obvious – to monitor platelet levels. Concomitantly requesting peripheral blood film is equally important because eltrombopag is suggested to cause bone marrow fibrosis in some cases. After having established the pre-eltrombopag treatment cellular morphology by a peripheral blood film, the subsequent films are done to monitor & compare the development of any new or worsening morphological abnormalities (e.g. teardrop cells, nucleated RBC’s or immature WBC’s). Any suggestion of bone marrow fibrosis and eltrombopag therapy should be stopped forthwith followed by a formal bone marrow biopsy. Besides the development of cellular morphological abnormalities, failure of platelet counts to ‘maintain’ after an initial positive response despite increasing the eltrombopag dose to the maximum level is another clue to the possible development of bone marrow fibrosis.

Eltrombopag is potentially hepatotoxic (usually mild and reversible transaminitis can develop) and is known to predispose to portal vein thrombosis even at normal/ subnormal platelet counts. In patients with Child-Pugh score $< 5$, eltrombopag therapy can be initiated and dose adjustments made just like any other patient with no hepatic impairment. If Child-Pugh score is $\geq 5$, eltrombopag should better be avoided. If benefits appear to clearly 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 dose adjustments are made on 2 weekly bases). 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 $\leq 50,000/\mu l$. Based on this, it is recommended that especially in patients with Caucasian ancestry, a dose of $> 50$ mg once daily should better be avoided/ used very cautiously in patients with Child-Pugh score of $\geq 5$; probably, the same holds true for people with other ethnic backgrounds like Pakistanis & Indians.

Eltrombopag is highly bound to plasma proteins predominantly to albumin and thus lacks any significant renal excretion (main route of excretion is via faeces). Based on this it is recommended that no dose adjustments need to be made in patients with renal impairment. Nonetheless, patients who already have renal impairment, need to be actively monitored for any further derangement (eltrombopag is known to have caused renal tubular toxicity in animal studies).

In patient’s $\leq 18$ years of age, eltrombopag therapy is not recommended because of the lack of clinical data.
Older patient’s ≥ 65 years of age should probably be treated similar to the younger subjects with no dose adjustments needed although more studies are needed in this age group to validate this recommendation.

6.9 Drug-drug Interactions
Antacids (containing aluminum & magnesium), high-calcium food (e.g. dairy products) & multi-vitamin tablets/ mineral supplements chelate and thus significantly reduce the systemic absorption of eltrombopag (Williams et al., 2009). It is therefore recommended that eltrombopag should be administered at least four hours before or after these products. In the unusual scenario of eltrombopag overdosage (→ ↑ LFT’s & ↑↑ platelet levels), oral administration of antacids and dairy products should be expected to limit eltrombopag absorption and cause increased faecal 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 needed it’s best to switch to low-dose atorvastatin or fluvastatin and actively monitor the patients for the development of any statin-related side effects (e.g. myositis). Caution should also be exercised when coadministering eltrombopag & methotrexate. Lopinavir/ritonavir (LPV/RTV) coadministration with eltrombopag seems to decrease oral absorption & thus bioavailability of the latter. If coadministration is necessary, platelet counts should be closely monitored to adjust the eltrombopag dose accordingly.

6.10 Safety Profile of Eltrombopag
Higher eltrombopag doses are associated with higher therapeutic efficacy & higher risk of side effects, & vice versa. Although almost 80% of the subjects on eltrombopag therapy develop one or the other 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, diarrhoea, constipation, insomnia, paresthesias, arthralgies, myalgias, peripheral edema) were of insufficient severity to require discontinuation of the drug. Potentially serious side effects of eltrombopag therapy that may require discontinuation of the drug include:

1. Thromboembolism (portal vein thrombosis, MI, CVA; DVT; PE).
2. Rebound thrombocytopenia after discontinuation of eltrombopag therapy with secondary increased risk of bleeding.
3. Hepatotoxicity.
4. Bone marrow fibrosis.

Eltrombopag has been found to cause thromboembolism especially portal vein thrombosis at normal or even subnormal platelet levels. Therefore, eltrombopag should only be used when benefits clearly outweigh the risks in the following ‘high-risk’ patient groups:

- Patients who already have evidence of hepatic impairment (Child-Pugh score ≥ 5).
- Patients who have known risk factors for thromboembolism e.g. deficiencies of Factor V Leiden, AT-III, protein C, protein S or antiphospholipid syndrome etc. Likewise patients with poor mobility (due to advanced senility, post-surgery/ trauma, morbid obesity etc), cancer patients and patients on OCP’s or HRT 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 $\geq 50,000/\mu l$. Ideally platelet count should not be allowed to rise above $100,000/\mu l$ 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-toward effect on platelet function as measured by platelet activation & aggregation, although more studies are needed to validate this observation (Erhardt et al., 2004; Provan et al., 2006). It has been postulated that both in HCV-related thrombocytopenia and CITP cases (regardless of whether treated with eltrombopag or not), the platelets become more ‘sticky’ and thus may aggregate and form a thrombus despite low counts (Haselboeck et al., 2012; Severinsen et al., 2011). A *rapid* increase in the platelet counts when eltrombopag is used in high doses of 75mg especially in patients with liver impairment probably also predisposes to thromboembolic events (TEEs). Additionally, an 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* (Cuker & Cines, 2010). There are conflicting reports in the literature regarding whether or not eltrombopag further increases this ‘physiological stickiness’ of platelets. Whereas, several case reports incriminated eltrombopag to have cause increased ‘reactivity’ of platelets with consequent increased propensity to aggregation and thrombus formation (Cuker, 2010), small recent in-vitro and in-vivo studies have refuted any such link (Erhardt et al., 2009; Psaila et al., 2012). The first in vivo report on TPO-RAs on platelet reactivity *only studied 20 patients* (Lambert, 2012). Therefore, more studies on larger cohorts of patients are needed to clarify this controversy that may have important implications in the future acceptibility & use of this drug.

In great majority of the patients the platelet counts fall to the pre-treatment levels within 2 weeks of stopping 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; also data on continued use of eltrombopag for $> 6$ months is very limited) (Bussel et al., 2010; Kuter et al., 2010; Saleh et al., 2009, 2010). Also, platelet counts should be monitored on weekly basis for at least 1 month following discontinuation of eltrombopag therapy. A recent study suggested that the observation of platelet counts returning to the baseline within 2 weeks post-treatment is based primarily on studies done in *CITP patients* (Afdhal, 2010; Cheng et al., 2011). In *CLD patients* with thrombocytopenia, platelet counts have been shown to *continue to increase* 1 week post-treatment and thereafter fall rather gradually (Kawaguchi). The exact underlying reason accounting 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 & for a few days post-treatment are generally *higher* than CITP patients (Gibiansky et al., 2011 Farrell et al., 2010). More studies are needed to demonstrate the likely *reduced* risk of bleeding in the immediate post-treatment period in CLD patients compared to CITP patients.

Eltrombopag has been incriminated to have caused bone marrow fibrosis in different studies. Although the exact mechanism is not yet established, it is thought to be the release of TGF-β from eltrombopag-activated megakaryocytes, which in turn causes a reversible increase in reticulin deposition (Ulich et al., 1996; Yanagida et al., 1997). This finding is backed by similar observations made in animal studies in which use of 2nd-generation TPO-RA was shown to cause extensive bone marrow fibrosis with secondary extramedullary hematopoiesis (a picture comparable to human myelofibrosis) (Douglas et al., 2002; Villeval et al., 1997; Yan, 1995). Because of relative paucity of data in human subjects, more long-
term exposure studies are needed to explore this potentially dangerous complication in humans (Arnold et al., 2009) (a 2-year, longitudinal bone marrow study (NCT01098487), which includes baseline and repeated bone marrow examinations is currently ongoing) (Mansoor et al., 2012). As mentioned before, if serial peripheral blood films suggest new or worsening cellular morphology indicating possible development of bone marrow fibrosis, it is one of the stopping criteria of eltrombopag therapy. Clinically, if platelet levels fail to improve or maintain despite optimal eltrombopag therapy in the recommended dosing range, we should suspect possible bone marrow fibrosis/impairment.

An association between autoimmune diseases and risk of development of hematologic malignancies is well established in medical literature (Stern et al., 2007). Autoimmune thrombocytopenia is known to be the first manifestation of a hematologic malignancy in many patients and actually may precede its onset by several years. Stimulation of hematopoietic stem cells by eltrombopag may thus increase the risk of development of hematologic malignancy, theretically speaking. Both pre-clinical studies (Erickson-Miller et al., 2007; Will et al., 2009) and EXTEND study (Mansoor et al., 2012) showed that eltrombopag does not promote proliferation of malignant cells and thus does not increase the risk of hematologic malignancy.

Despite of some conflicting reviews in the literature, it is the opinion of this author that pregnancy be regarded as an ‘absolute’ contraindication for interferon, ribavirin 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 &/or embryocidal effects in animal studies and the potential risks in humans are unknown at this stage. Likewise, lactating mothers should not be offered any of these three agents because whereas the risk in human subjects is unknown, we know from animal studies that all three of these agents are likely secreted in the milk.

Eltrombopag doesn’t appear to prolong QT interval in healthy subjects in doses between 50 – 150 mg in comparison to the placebo.

7 Cost-effectiveness of Eltrombopag Therapy

In UK one 50 mg tablet of eltrombopag costs £55, which makes one month course at 50 mg once daily dose cost £1650 (although due to negotiated procurement discounts the precise cost on ground may vary). Not much data is available on the cost-effectiveness of this novel agent in the treatment of ‘HCV-related’ thrombocytopenia; nonetheless, a recent National Institute of Health & Clinical Excellence (NICE), UK technology appraisal on the use of eltrombopag in ‘CITP’ patients concluded that eltrombopag is not a cost-effective use of NHS resources (Bowers et al., 2009). 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 QALY gained for splenectomised people to £90,471 per QALY gained for non-splenectomised people. The highest ICER reported was £99,441 per QALY gained for the non-splenectomised population (based on the acquisition cost of £60 per 50 mg tablet). The lowest ICER reported was £69,301 per QALY gained for the splenectomised 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 (Boyers et al., 2012).
8 Future considerations

1. Good quality RCTs need to be done regarding the role of eltrombopag in the treatment of ‘HCV-related’ thrombocytopenia specifically.

2. More studies on larger cohorts of patients are needed to clarify whether or not eltrombopag causes increased *in-vivo* platelet reactivity (stickiness) and thus predisposes to thromboembolism.

3. Studies directly comparing eltrombopag with romiplostim (another TPO-RA) are needed to determine their relative therapeutic efficacies, safety profiles and cost-effectiveness. *Indirect* comparison of the data from RAISE trial suggested that eltrombopag is probably less efficacious than romiplostim (the latter has recently been approved by NICE, UK for use in CITP).

4. More head-on studies are needed to compare the relative therapeutic efficacies, safety profiles and cost-effectiveness of the ‘continuous’ vs. ‘intermittent’ dosing schedules of eltrombopag.

5. More long-term exposure studies & pharmacovigilance activities are needed to specifically explore the safety concerns of 2nd-generation thrombopoietic growth factors (eltrombopag; romiplostim) on bone marrow function in human subjects, hepatotoxicity, TEs, recurrence of thrombocytopenia following cessating eltrombopag therapy, potential for increase in hematologic malignancies, cataracts/phototoxicity, renal tubular toxicity, & endosteal hyperostosis.

9 Conclusion

Although more studies are needed to validate true indications, dosage schedule, therapeutic efficacy and safety profile of eltrombopag adjunct therapy in HCV-related thrombocytopenia, from our knowledge of the use of this novel agent in CITP, it appears that it is an efficacious treatment modality for short-term amelioration of thrombocytopenia (Ikeda et al., 2009). There are some relatively serious safety concerns related to the use of this drug in CLD patients, particularly treatment-related thrombosis. It doesn’t 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 peri-procedural period is being made, this drug should normally be used for short-term periods of ~ 2 weeks and in the lowest possible effective doses (usually 12.5-50 mg once daily in CLD patients). At least at the time of writing this article, eltrombopag doesn’t seem cost-effective (Tillmann et al., 2009).

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