Thrombocytopenia and Procedural Prophylaxis in the Era of Thrombopoietin Receptor Agonists

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Thrombocytopenia is common in patients with advanced liver disease. These patients frequently require invasive diagnostic or therapeutic procedures in the setting of thrombocytopenia. A common platelet goal before such procedures is ≥50,000/μL, but target levels vary by provider and the procedure. Platelet transfusion has disadvantages, including safety and cost. No other short-term options for ameliorating thrombocytopenia before procedures were available until the thrombopoietin receptor agonists were recently approved. Avatrombopag and lusutrombopag can be used in certain patients with thrombocytopenia due to advanced liver disease undergoing elective invasive procedures; these new agents are highly effective in carefully selected patients, and real world data of safety and efficacy are awaited. (*Hepatology Communications* 2019;3:1423-1434).

Thrombocytopenia and coagulopathy are frequently observed in patients with advanced liver disease. Such patients present a challenge when they require an invasive diagnostic or therapeutic procedure as these hemostatic abnormalities may increase the risk of bleeding complications. Yet, such procedures are frequently needed. By the Baveno criteria, thrombocytopenia alone in patients with cirrhosis is an indication for screening endoscopy to assess for esophageal varices.[1] Many nonendoscopic procedures are also required in such patients, especially in those with hepatocellular carcinoma (HCC) and other complications of cirrhosis or those undergoing liver transplantation evaluation.

Thrombocytopenia is defined as serum platelet count <150,000/μL and is stratified into mild, moderate, and severe (corresponding to platelet counts >75,000, 50,000-75,000, and <50,000/μL, respectively).[2] Thrombocytopenia is extremely common in patients with advanced liver disease; up to 76% of patients with cirrhosis have mild thrombocytopenia, 13% have a moderate degree, and severe thrombocytopenia is present in 1%.[3] The degree of thrombocytopenia also correlates with both the severity of liver disease as well as long-term outcomes.[3]

Historically, thrombocytopenia in the periprocedural setting has been corrected with a transfusion of platelets, either immediately before or during the procedure. However, two new oral thrombopoietin (TPO) receptor agonists were recently approved to increase platelet counts in the outpatient setting and thus avoid platelet transfusions. The following review will discuss the current management strategies for periprocedural thrombocytopenia, including platelet transfusions and the role of TPO receptor agonists.

Abbreviations: CrCl, creatinine clearance; CTP, Child-Turcotte-Pugh; ERCP, endoscopic retrograde cholangiopancreatography; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; PVT, portal vein thrombosis; TEG, thromboelastography; TPO, thrombopoietin.

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Pathophysiology of Platelets in Liver Disease

In advanced liver disease, platelet levels are reduced by several mechanisms.[2,4] The most common cause is splenic sequestration resulting from portal hypertension. The finding of thrombocytopenia in patients with cirrhosis is so highly suggestive of the presence of portal hypertension that current endoscopy guidelines use platelet counts as a criterion for gastroesophageal variceal screening.[1] Although splenic sequestration is the main cause of thrombocytopenia, increased platelet destruction also occurs by direct splenic destruction and immune-mediated production of autoantibodies. Another mechanism of thrombocytopenia in this setting is underproduction of platelets. Hepatocellular dysfunction leads to lower production of TPO, and bone marrow suppression may occur from untreated hepatitis C virus, alcohol use, nutritional deficiencies, infections, and medications. Finally, dilutional thrombocytopenia occurs with volume resuscitation by crystalloid, colloid, or massive blood transfusions.[2,4]

In addition to the reductions in the absolute number of platelets, derangements of platelet function also occur and worsen with the degree of liver dysfunction and Child-Turcotte-Pugh (CTP) class.[5] Intrinsic platelet function defects include defective adherence to injured vessels, decreased aggregation, decreases in transmembrane signaling, and reduction in response to signaling stimuli.[5,6] Circulating agents, such as apolipoprotein E, bile salts, and fibrinogen degradation products, contribute to platelet dysfunction.[6] Additional factors that adversely impact platelet function include uremia, medications, sepsis, and nutritional deficiencies.

Despite the reduction in platelet number and function, patients with advanced liver disease have an increased risk of thrombotic events, particularly in the portal circulation[7] where blood flow velocity is reduced. Thrombosis in the setting of advanced liver disease is promoted by increases in the von Willebrand factor, which augments platelet adherence, as well as decreases in the enzyme a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS 13), which inhibits the von Willebrand factor. Decreases in the anticoagulant factors antithrombin and protein C and elevated levels of procoagulant factor VIII also promote thrombosis. Finally, fibrinolysis is also inhibited by decreases in plasminogen and increases in plasminogen activator inhibitor.[7]

Thus, it is now widely accepted that a delicate balance between prohemostatic and antihemostatic forces exists in advanced liver disease; standard laboratory measures, including prothrombin time, partial thromboplastin time, and platelet count, do not accurately predict the risk of bleeding and thrombosis.[7,8] Although thrombocytopenia has been variably associated with procedure-related bleeding risk,[9,10] other *in vitro* data in patients with cirrhosis suggest sufficient thrombin generation occurs when platelet levels are ≥56,000/μL.[11] Given these data discrepancies as well as the difficulty in correlating standard laboratory values to the bleeding and thrombosis risks in individual patients, thromboelastography (TEG) or rotational thromboelastography (ROTEM) as well as sonorheometry (collectively known as whole-blood viscoelastic testing [VET]) may have a role in patients with advanced liver disease.[12] VET measures parameters of clot formation and dissolution and can be used to determine which (if any) blood products are

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necessary to reduce bleeding risk. Use of intra-operative TEG is standard during liver transplantation,[13] and in some centers TEG may be used before elective procedures to guide transfusion choices. Despite its potential utility, prospective studies to establish specific criteria remain lacking.

Considerations for Providers Treating Thrombocytopenic Patients

Although published society guidelines provide direction on management of periprocedural thrombocytopenia, most health care providers maintain a rather individualized approach. Many factors are integrated into the decision whether to proceed with the procedure or to augment the platelet count before the procedure, including elements specific to the patient, to the procedure, and to the provider. Patient factors include the degree of thrombocytopenia; presence or absence of concurrent coagulopathy; recent use of medications that may affect hemostasis, such as antiplatelet agents or anticoagulants; prior history of bleeding with procedures; and when applicable, the degree of thrombocytopenia or coagulopathy at which prior bleeding occurred.

Procedure-specific factors include the nature of the planned procedure and its known bleeding risks in the general population as certain procedures have higher risks than others. The severity of potential outcomes if bleeding occurs and the availability of treatment options for bleeding must also be considered. For example, severe bleeding from a neurologic procedure may have much greater morbidity and sequelae than bleeding from a colon polypectomy. The procedure location is also relevant; stand-alone outpatient centers may not have an adjacent emergency unit or readily available surgical expertise if severe bleeding occurs.

Finally, factors specific to the provider include current institutional protocols and local practices, prior training methods, degree of experience, personality (degree of risk aversion), and overall medical style. The local medical–legal culture and patient population demographics may also influence provider preference. Thus, the wide variations seen in medical practice of target preprocedural platelet levels can be explained by the individualized integration of all these factors.

Recommended Platelet Goals for Procedures

ENDOSCOPY

Current American Society for Gastrointestinal Endoscopy (ASGE) guidelines support obtaining routine pre-endoscopy platelet assessment in patients with high risk for thrombocytopenia, such as advanced liver disease, but the minimum platelet count necessary for safely performing endoscopic procedures in any patient (regardless of liver disease) has not been definitively determined.[14] Data suggest diagnostic upper endoscopy can be safely performed at platelet levels ≥20,000/μL,[15] and many endoscopists are comfortable with mucosal biopsies and variceal banding at this level. However, other studies suggest platelet goals ≥50,000/μL for endoscopic biopsies. As guidelines do not specify a strict threshold for upper endoscopy,[15] endoscopists act based on their preference. For lower endoscopy, many adopt the same parameters as upper endoscopy.

There are also no specific platelet guidelines for all other endoscopic procedures. Procedures are categorized by the ASGE into high and low risk for bleeding[8,16] (Table 1), but such bleeding risks apply to the general population and are not specific to patients with advanced liver disease. As discussed above, strategies are often individualized, but many providers default to target platelet counts ≥50,000/μL for higher risk procedures, such as large polypectomy, endoscopic treatment of hemorrhage, endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy, or endoscopic ultrasound with fine needle aspiration. In contrast, others perform prophylactic variceal band ligation or ERCP with balloon dilation at lower platelet counts.

PARACENTESIS

In patients with advanced liver disease, diagnostic and/or therapeutic paracentesis are extremely common procedures. Fortunately, paracentesis is low risk

TABLE 1. PROCEDURE RISKS AND PLATELET TARGETS

Procedure	Suggested Platelet Target‡	Use of TPO Agents
Low risk	≥20,000/μL	Use as needed (depending on provider preferences‡) in patients with platelet counts <20,000/μL
paracentesis		
EGD or colonoscopy, mucosal biopsies*		
prophylactic variceal banding*		
small polypectomy*		
capsule endoscopy		
push enteroscopy		
diagnostic balloon enteroscopy		
ERCP with balloon dilation or stent		
EUS without FNA		
enteral stent deployment†		
argon plasma coagulation, Barrett's ablation		
central line placement		
bone marrow biopsy		
bronchoscopy without biopsy		
thoracentesis		
transjugular liver biopsy†		
Moderate risk	≥50,000/μL	Recommended with monitoring of platelets
percutaneous liver biopsy		
larger polypectomy		
endoscopic mucosal resection or submucosal dissection, ampullectomy		
cystgastrostomy		
percutaneous endoscopic gastrostomy or jejunostomy tube		
endoscopic pneumatic/Bougie dilation		
endoscopic tumor ablation		
ERCP with sphincterotomy		
locoregional therapy of HCC		
thoracentesis		
percutaneous IR-guided organ biopsy		
diagnostic lumbar puncture		
cardiac catheterization		
surgical procedures (non-neuroaxial)		
High	≥100,000/μL	Use with caution with monitoring of platelets during the dosing period; discontinue if significant overcorrection
intracranial and spinal procedures		

*Based on endoscopist preference.
†Controversial, some consider higher risk.
‡Providers may have differing goals based on the procedure (such as paracentesis may be a lower bleeding risk than polypectomy).
Abbreviations: EGD, esophagogastroduodenoscopy; EUS, endoscopic ultrasound; FNA, fine needle aspiration; IR, interventional radiology.

for bleeding, with estimates of hemorrhage in 1 per 1,000 patients. A study of large volume paracenteses in 1,100 patients who were not given preprocedure transfusions to correct laboratory abnormalities did not show any bleeding complications despite severe thrombocytopenia and coagulopathy; 54% of patients had platelet counts <50,000/μL and as low as 19,000/μL.[17] As such, guidelines do not suggest routinely correcting thrombocytopenia before paracentesis.[18]

PERCUTANEOUS LIVER BIOPSY

In contrast to paracentesis, percutaneous liver biopsy has a higher risk for bleeding. Significant bleeding requiring transfusion after liver biopsy

occurs in one per 2,500-10,000 cases in patients with underlying liver disease, whereas less severe bleeding not requiring transfusion may occur in up to one in 500.[19] In the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial, over 2,700 biopsies were performed in patients with fibrosis or cirrhosis. Bleeding rates of 5% occurred when platelets were <60,000/μL versus under 1% at higher platelet levels.[20] In general, a threshold platelet count ≥50,000/μL is frequently sought for percutaneous liver biopsy. Transjugular liver biopsy is an alternative, but the transjugular approach also has bleeding risks.

OTHER PROCEDURES

Transfusion of platelets for procedures performed by providers from many other specialties is supported by society guidelines, with platelet goals ≥50,000/μL widely recommended for many procedures.[21-23] However, most procedures have not been studied specifically in patients with advanced liver disease. Furthermore, different specialists may have disparate platelet goal preferences for the same procedure. For example, bedside thoracentesis or central venous catheter insertion is often performed by internists or intensivists at lower platelet counts, whereas interventional radiologists often prefer platelets ≥50,000/μL. The latter is most likely due to adherence to guidelines from the Society of Interventional Radiology recommending platelet transfusion for all percutaneous procedures, regardless of specific procedure-related bleeding risk, when the platelet count is <50,000/μL.[24] This threshold is also supported by 2013 American Society of Hematology guidelines that suggest targets ≥50,000/μL for any patient undergoing an invasive procedure within the next 4 hours.[23] These guidelines have recently been critiqued.[25]

Procedure exceptions to the ≥50,000/μL platelet count threshold include bone marrow biopsy and placement of central venous catheters, for which a platelet count ≥20,000/μL is acceptable. Another exception may be dental procedures; data suggest that platelet transfusion is not necessary for tooth extraction in patients with cirrhosis as local hemostatic techniques or intranasal desmopressin can be employed instead.[26,27] Yet, a platelet count threshold ≥50,000/μL is often used. For lumbar puncture and non-neurologic surgery, platelet counts ≥50,000/μL are acceptable,[22] but higher platelet goals (closer to 100,000/μL) are recommended in patients with neurosurgical needs.[23]

Current Standards of Care: Platelet Transfusions for Thrombocytopenia

In patients without cirrhosis, a standard unit dose of platelets can be infused over 20 to 30 minutes and typically raises the platelet count by approximately 30,000/μL within 10 minutes of transfusion.[21] Platelet counts are highest within the first hour of transfusion and gradually decline over days. These effects are blunted in patients with cirrhosis in whom a single dose raises platelets by an average of only 12,000/μL, although this amount has been shown to improve clot firmness measured by ROTEM.[28] Whether platelets should routinely be remeasured after infusion remains unestablished.

Platelet transfusion has several disadvantages, with medical harm being the most concerning. Risks include febrile transfusion reactions, allergic or hypersensitivity reactions, transfusion-related acute lung injury or transfusion-associated circulatory overload, infections (bacterial, viral, parasitic), hemolysis secondary to blood group ABO minor incompatibilities, and transfusion-associated graft versus host disease.[21]

A longer term risk of platelet transfusions is alloimmunization, the formation of antiplatelet antibodies. Risk increases with the total number of transfusions. Alloimmunization may result in platelet counts failing to adequately rise after transfusion (refractoriness). In this setting, matched platelets can be used, but delays frequently occur due to availability. Importantly, alloimmunization and refractoriness may pose difficulties in patients who later undergo liver transplantation or other major surgeries that require large numbers of platelet transfusions. In fact, some patients are excluded from liver transplantation because of significant antiplatelet antibodies from prior platelet transfusions.

In addition to safety, other challenging considerations for elective platelet transfusions include cost and logistics. In many cases platelets must be given in the hospital or at a transfusion center to allow

close monitoring and rapid posttransfusion laboratory assessment. Storage and shelf life, lack of availability of matched platelets, and patient scheduling are other key factors indicating that platelet transfusions in this setting are not ideal.

TPO Physiology and History of TPO Receptor Agonists

Alternative strategies for management of thrombocytopenia have been sought. The discovery of the growth factor TPO and development of TPO receptor agonists were exciting breakthroughs for thrombocytopenia management.

TPO was cloned in 1994[4] and was found to be the main promoter and regulator of platelet production. TPO is produced primarily in hepatocytes and in smaller amounts in the kidney and bone marrow.[2] Circulating TPO binds to a receptor on platelet and megakaryocyte membranes to prevent apoptosis and increases the number, size, and differentiation of megakaryocytes and platelets,.[2,29]

Production of TPO by hepatocytes is decreased in advanced liver disease and thus contributes to thrombocytopenia in this setting. Plasma TPO concentrations are lower in patients with cirrhosis and thrombocytopenia,[30] and platelet response to TPO is also reduced.[31] Both TPO and platelet levels increase after liver transplantation[32] and splenic embolization.[33] In fact, splenic embolization or surgical splenectomy has been employed by some centers to address severe thrombocytopenia, but due to the associated risks, these procedures are debatable and not widely recommended.

The discovery of TPO led to interest in development of a therapeutic target for patients with thrombocytopenia. However, the original agents (a recombinant human TPO and a pegylated recombinant human megakaryocyte growth and development factor) were limited due to formation of cross-reacting antibodies that inhibited endogenous TPO and created severe thrombocytopenia in 10% of patients.[2,4] Later, peptide and nonpeptide TPO receptor agonists were developed that are structurally dissimilar to TPO and circumvent issues with antibodies.[4]

Current TPO Receptor Agonists

The first successful TPO receptor agonists developed were romiplostim and eltrombopag. Romiplostim (Nplate, Romiplate) is indicated for thrombocytopenia due to hematologic disorders. Small studies and case reports exist in patients with liver disease,[34-36] but safety concerns for portal vein thrombosis (PVT) have been raised.[37] Eltrombopag (Promacta, Revolade) was previously used in patients receiving interferon treatment for hepatitis C when thrombocytopenia otherwise limited treatment.[38] Due to occurrence of PVT[38,39] and hepatotoxicity, eltrombopag is no longer commonly used in patients with liver disease.

However, two nonpeptide TPO agonists, avatrombopag and lusutrombopag, were recently approved for use in patients with advanced liver disease and thrombocytopenia who undergo elective procedures. Avatrombopag (Doptelet) was approved in the United States in May 2018.[40,41] In the global, multicenter, combined ADAPT-1 and ADAPT-2 phase III, randomized, double-blind, placebo-controlled clinical trials, avatrombopag given at 40 or 60 mg daily (based on initial platelet counts) for 5 days before an elective procedure increased the platelet count and reduced platelet transfusion requirements.[40] A total of 231 patients were included in the ADAPT-1 and 204 patients in the ADAPT-2 trials. Platelet counts were measured during the screening period as well as on treatment day 1 and at the time of the procedure and 7 and 35 days after the procedure. The primary endpoint for each was the proportion of patients who did not require platelet transfusion or a rescue procedure for bleeding from randomization to 7 days after the procedure. Secondary endpoints included the number of patients who reached platelet counts of >50,000/μL and the change in platelet value from baseline to the date of procedure. The procedure bleeding risks included mostly low risk procedures (61% of patients) as well as procedures with potentially higher bleeding risk (e.g., liver biopsy, transjugular intrahepatic portosystemic shunt). No neurologic (intracranial or intraspinal) procedures were included. Given the aforementioned safety concerns of PVT with eltrombopag, the ADAPT-1 and ADAPT-2 trials excluded patients at highest risk of forming PVT (history of thrombosis, current portal or mesenteric thrombosis

at screening or decreased portal vein velocity, or advanced HCC).

Treatment groups in the ADAPT-1 and ADAPT-2 trials achieved the primary endpoints (platelet count >50,000/μL and no procedure-related bleeding events) in 65% of patients with lower baseline platelets (<40,000/μL) and in 87% of patients with baseline platelet counts 40,000-49,000/μL, whereas placebo response rates were 22%-38%. The difference in the treatment group compared to placebo in both trials was statistically significant ($P < 0.0001$ for ADAPT-1, $P = 0.006$ for ADAPT-2). For both trials, the difference between the number of patients achieving target platelet counts for the study drug compared to placebo was most striking in patients with higher baseline platelet counts (who received the lower dose of avatrombopag), and results did not differ by procedure bleeding risk.

The secondary outcome in both trials (percentage of patients who reached platelets >50,000/μL) was 69% versus 4% for ADAPT-1 and 67% versus 7% for ADAPT-2. The mean change in platelet count in the lower platelet count group was 32,000/μL in the avatrombopag group and 800/μL in the placebo group for ADAPT-1 and 31,000/μL versus 3,000/μL for ADAPT-2. In the higher baseline group, the mean increase was 37,000/μL versus 1,000/μL for ADAPT-1 and 45,000/μL versus 6,000/μL for ADAPT-2. Platelet counts increased by day 4 of treatment and peaked around days 10-13; by day 35, they returned to baseline.

Overall safety parameters were favorable. With careful patient selection, 1 patient who received avatrombopag (40 mg) in the ADAPT-1 trial was found to have a partial PVT on day 18 (13 days after last dose), which was deemed nonserious. The thromboembolic rate between both the ADAPT-1 and ADAPT-2 trials was not different from the placebo group for either dose of study drug.[40]

The newest agent available in the United States is lusutrombopag (Mulpleta), which has been used in Japan since 2015 to increase platelet counts in patients with advanced liver disease.[42] It has been used frequently in Japan in patients with cirrhosis with thrombocytopenia undergoing partial splenic embolization[43] and locoregional treatment of HCC,[44-47] and case reports suggest efficacy and safety of repeated courses 3-4 months apart.[44,45]

In the United States, lusutrombopag was also approved for use in patients with advanced liver disease in whom an elective procedure is planned, based on two randomized, double-blind, placebo-controlled clinical trials (the L-PLUS-1 and L-PLUS-2).[48,49] These studies demonstrated the efficacy of lusutrombopag in increasing platelet count and reducing the need for platelet transfusions in patients with chronic liver disease and thrombocytopenia undergoing invasive procedures.

The L-PLUS-1 and L-PLUS-2 studies were both multicenter, randomized, double-blind, placebo-controlled phase III clinical trials comparing lusutrombopag 3 mg to placebo. A total of 97 patients in the L-PLUS-1 and 215 patients in the L-PLUS-2 trials were randomized. Unlike in the avatrombopag trials, a uniform dosage of lusutrombopag 3 mg daily for up to 7 days was used. Platelet counts in both trials were checked at screening, baseline (day 1), and at days 5-8 and at frequent intervals after day 8 through day 35. The drug was stopped if the platelet count reached >50,000/μL or increased by >20,000/μL on days 5-7. Procedures were performed on days 9-14. The primary endpoint was the proportion of patients who did not require platelet transfusions before the procedure (both studies) or rescue transfusions for bleeding within 7 days of the procedure in the L-PLUS-2 study. For L-PLUS-1, secondary endpoints included the proportion of patients who reached target platelet counts (≥50,000/μL and with an increase >20,000/μL), the duration of the sustained platelet count increase, and the time course of platelet count changes. Secondary endpoints for L-PLUS-2 included the proportion of patients that required no platelet transfusion during the study period, the proportion that reached target platelet counts (≥50,000/μL and with an increase >20,000/μL) at any time during the study, the number of days at which platelet counts remained ≥50,000/μL, the proportion that needed rescue therapy for bleeding, frequency of platelet transfusions, and platelet count over time. In both studies, a variety of procedures were included, including liver biopsies, treatment of varices, and various tumor-directed therapies; no intracranial or intraspinal procedures were included. Notably, unlike the other TPO receptor agonists previously mentioned, in both the L-PLUS-1 and L-PLUS-2 trials, PVT was evaluated with ultrasound both before and after drug dosing.

In the L-PLUS-1 trial, 79% of the lusutrombopag group and 12.5% of the placebo group achieved platelet counts ≥50,000/μL ($P < 0.0001$) and thus required

no transfusions. The proportion who achieved the target platelet count and had an increase >20,000/μL was 77% versus 6%; over 50% of these responders in the lusutrombopag group maintained the platelet target by days 10-17. The median platelet count reached ≥50,000/μL after 5 days, with peak counts achieved at a mean of 13 days. The average number of days (without platelet transfusions) that the platelet counts remained ≥50,000/μL was 21 days in the lusutrombopag group versus 6 days (with platelet transfusions included) in the placebo group.

In the L-PLUS-2 trial, 65% versus 29% placebo did not require platelet transfusion or a rescue procedure to treat bleeding ($P < 0.0001$).[49] The proportion who achieved platelet counts ≥50,000/μL with an increase by >20,000/μL was 70% versus 14%, and the median duration of platelets remaining ≥50,000/μL was 19 days versus 0 days. The median maximum change in platelet count was 45,000/μL versus 11,000/μL.

One PVT occurred in a patient on lusutrombopag in the L-PLUS-1 trial that was deemed probably related to the drug (as opposed to directly related to the procedure itself). In the L-PLUS-2 study, 1 patient in the lusutrombopag arm had an intrahepatic arterial thrombosis deemed unrelated to the drug; no PVT was demonstrated. The overall thrombosis rate in both trials was not statistically different between treatment and placebo groups.

Dosing and Pharmacology of TPO Receptor Agonists

TPO agonists are effective in increasing platelet count for a longer duration than platelet transfusions. Platelet counts rapidly rise after 5 days of avatrombopag, peak at day 10, and return to baseline levels by about 1 month.[40] For lusutrombopag, the median duration of platelet counts remaining ≥50,000/μL is 19-22 days.[48,50,51] Because of the longer lasting rise in platelets, use of these agents can allow either repetition of procedures or postponement without repeat dosing.

Both agents are metabolized primary by the hepatic cytochrome p450 system. Avatrombopag was studied in patients with cirrhosis with CTP classes A, B, and C with Model for End-Stage Liver Disease (MELD) scores of ≤23. No hepatic dose adjustment is needed. Lusutrombopag was studied in patients with cirrhosis with CTP classes A and B and also requires no hepatic dose adjustment. In patients with concomitant mild or moderate renal disease (creatinine clearance [CrCl] >30 mL/minute), neither avatrombopag nor lusutrombopag require renal dose adjustment. Insufficient data exist for use of these agents in patients with CrCl <30 mL/minute.[50,52]

Neither avatrombopag nor lusutrombopag was studied for use in the pediatric population. There are insufficient data to inform pregnancy risks; animal studies suggest potential fetal harm at highly supratherapeutic doses. Neither is recommended for use in lactating women. Finally, in cases of overdose, no antidotes are available (including hemodialysis), and rapid increases in platelet counts theoretically could be associated with PVT.[50,52]

Logistical Aspects of TPO Agonists

The logistical aspects of prescribing TPO agents, such as costs and insurance company approval, are highly variable and frequently changing. To our knowledge, no published studies have evaluated the costs of platelet transfusions to either lusutrombopag or avatrombopag. However, a small study evaluating romiplostim and eltrombopag for patients with chronic liver disease undergoing percutaneous liver biopsy demonstrated that the cost of platelet transfusion was significantly greater than the cost of either agent ($7,500 for platelets vs. $2,284 for romiplostim and $2,991 for eltrombopag).[53] Given that both avatrombopag and lusutrombopag were only recently approved and are still "new" to insurance companies, it may be prudent to prescribe these agents a few weeks in advance of the procedure date to allow time for any prior authorizations or other delays.

Author Recommendations for Preprocedural Thrombocytopenia

TPO receptor agonists are indicated for stable nonbleeding patients with cirrhosis with severe

thrombocytopenia undergoing planned elective procedures. For reasons noted above, TPO agonists are preferable to platelet transfusions if possible. The procedure date must be known far enough in advance to obtain the medication in the proper time frame. We suggest that the patient's health care provider determine whether TPO receptor agonists are appropriate for specific patients depending on the nature of the planned procedure, baseline platelet count, and the platelet goals of the provider performing the procedure.

Avatrombopag is dispensed in 20 mg tablets, and dosing is determined by baseline platelet count (Table 2); 40 mg is used if platelets are 40,000-49,000/μL, and 60 mg is used if platelets are <40,000/μL. Each dose is taken once daily for 5 days and should be started 10-13 days before the scheduled procedure. The procedure should then be completed 5-8 days after the last dose per prescribing guidelines.[52] Lusutrombopag is dispensed in 3-mg oral tablets and is a uniform dose regardless of baseline platelet count. It is administered once daily for 5-7 days before a procedure, which should be performed 2-8 days after the last dose[50] per prescribing guidelines. However, procedure timing is at the discretion of the providers and could be performed outside these studied time windows if the platelet count is above the goal.

Prescribing guidelines do not outline a specific laboratory monitoring plan other than measuring platelet counts on the day of the procedure or the day immediately before.[50,52] In patients in whom platelets do not reach the goal despite treatment, platelet transfusion can be given. For some endoscopic cases, alteration of the procedure to reduce bleeding risk may allow completion at a lower platelet count without treatment (i.e., ERCP without sphincterotomy or colonoscopy without removal of large polyps). Finally, in settings of patients who are awaiting liver transplantation, some elective procedures are best delayed until after transplantation when platelet counts improve.

When TPO receptor agonists are used, every effort must be taken to ensure that the procedures are not delayed as platelet counts will decrease. If the procedure is delayed, platelet counts should be rechecked. Extended dosing (longer courses) of TPO receptor agonists for this setting were not studied.

We suggest avoidance of TPO receptor agonists or use with extreme caution in certain patients (Table 3), including those with MELD scores >24 (or CTP class C for lusutrombopag), and in patients on dialysis, as such patients were excluded from the trials. Unfortunately, those with high MELD and CTP scores may be more likely to require invasive diagnostic procedures, especially if undergoing liver transplantation workup, and are also most likely to have severe thrombocytopenia. In addition, caution or avoidance is suggested for patients with inherited hypercoagulable disorders and patients at highest risk of PVT (patients who have known current or prior thrombus in the portal or mesenteric circulation, documented decreased portal vein velocity, and Budd Chiari syndrome). Pregnancy is considered a hypercoagulable state and thus may increase the risk of PVT; TPO receptor agonists in this setting are best avoided.

In addition to patient selection factors, the baseline and goal platelet counts and the nature of the procedure can help inform when TPO receptor agonists are most useful. The risks and benefits of treatment with TPO agonists must be considered as well as the inherent risks of platelet transfusion in each particular clinical setting. For procedures with lower bleeding risk performed at lower platelet counts (<50,000/μL), the use of a TPO receptor agonist is not generally necessary unless there is a higher suspected bleeding risk (i.e., prior history of bleeding with a similar procedure). For higher risk procedures, if the platelet count is low, use of a TPO receptor agonist is supported.

The novelty of TPO receptor agonists and relatively short time frame of clinical availability leaves yet unanswered questions. For example, dosing for platelet count thresholds of ≥20,000/μL has not

TABLE 2. DOSAGE/TIMING OF TPO RECEPTOR AGONISTS

	Avatrombopag	Lusutrombopag
Platelets <40,000/μL	60 mg PO daily × 5 days (day 1, first dose)	3 mg PO daily × 5-7 days (depending on platelet count at day 5)
Platelets 40,000-49,000/μL	40 mg PO daily × 5 days	3 mg PO daily × 5-7 days (depending on platelet count at day 5)
Platelets >50,000/μL	Not studied	Not studied

Abbreviation: PO, per oral (by mouth).

TABLE 3. RELATIVE AND ABSOLUTE CONTRAINDICATIONS TO TPO RECEPTOR AGONISTS

Absolute Contraindications	Relative Contraindications*
• Hypersensitivity reaction to prior TPO receptor agonist • Known current or prior portal vein/mesenteric system thrombosis • Pregnancy	• Renal insufficiency (on dialysis or CrCl <30) • MELD score >24 or CTP C (lusutrombopag) • Inherited hypercoagulable state • Platelet counts >50,000/μL • Advanced HCC (Barcelona class C/D) • Prior platelet transfusion within 7 days • Slow portal vein flow (<10 cm/second) • Budd Chiari or sinusoidal obstructive syndrome

*Many are not well studied.

been determined; in addition, they were not studied for patients who require target goals of ≥100,000/μL but with baseline platelet counts of >50,000/μL. Furthermore, the frequency of laboratory monitoring to ensure that platelets do not significantly overcorrect and increase the risk of PVT is also undefined. Finally, whether patients should undergo a screening Doppler ultrasound to ensure patency of the portal vein before prescribing a TPO agonist is uncertain but seems prudent. These clinical questions will require further study, and additional postmarketing data on drug safety are awaited.

Concluding Remarks

Thrombocytopenia is common in patients with advanced liver disease, yet these patients frequently require procedures. A platelet count ≥50,000/μL is a frequent target. Platelet transfusion in the elective preprocedural setting has disadvantages of safety and cost but remained the only short-term option for thrombocytopenia until the recent TPO receptor agonists were approved.

TPO agonists are efficacious and well tolerated. They are useful in most (but not all) patient populations with thrombocytopenia and advanced liver disease. As these agents do not have an immediate effect on platelet counts, their roles are largely limited to the outpatient setting in which procedures are planned in advance. There are no society-endorsed clinical guidelines for use as of yet. Additional study of use in the sickest population groups with CTP class C, MELD scores of 24 or higher, and patients on hemodialysis are awaited.

Despite these limitations, TPO receptor agonists represent an optimal alternative to severe thrombocytopenia in patients with cirrhosis in the preprocedural setting and thus reduce the use of platelet transfusion and costs.

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