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REVIEW

Management of Thrombocytopenia in Patients with Chronic Liver Disease

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Abstract

Background Thrombocytopenia is the most common hematologic complication associated with chronic liver disease (CLD) with important clinical implications. While the mechanisms for thrombocytopenia are multifactorial, platelet sequestration in the spleen and decreased thrombopoietin (TPO) production are the main mechanisms in patients with CLD.

Aim This review outlines the current treatment options for thrombocytopenia in patients with CLD, explores their limitations, and proposes a revised treatment algorithm for the management of thrombocytopenia in this patient group.

Methods A PubMed search of the literature was undertaken with search terms focused on CLD and thrombocytopenia.

Results Until now, the standard-of-care treatment in these patients has been the use of platelet transfusions either prophylactically or periprocedurally to control bleeding. Treatment options, such as splenic artery embolization and splenectomy, are invasive, and their utility is limited by significant complications. The US Food and Drug Administration recently approved 2 s-generation TPO-receptor agonists, avatrombopag and lusutrombopag, as safe and effective therapies for the treatment of thrombocytopenia in patients with CLD scheduled to undergo a procedure.

Conclusions The addition of avatrombopag and lusutrombopag offers physicians an alternative to platelet transfusions in patients with CLD who have to undergo medical/dental procedures that could potentially put them at an increased risk of bleeding. There are several other drugs in the research pipeline at various stages of development, including a new class of monoclonal antibodies that can bind to and activate TPO-receptor agonists. The outlook for treatment choices for thrombocytopenia in patients with liver disease is promising.

Keywords Chronic liver disease · Cirrhosis · Thrombocytopenia · Thrombopoietin receptor agonists · Platelets transfusion · Treatment algorithm

Introduction

Thrombocytopenia, defined as a platelet count below 150,000/μL, is the most common hematological complication in patients with chronic liver disease (CLD) [1, 2]. Thrombopoietin (TPO) production and splenic platelet sequestration are the main mechanisms for the development of thrombocytopenia in patients with CLD [3, 4].

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In the USA, nearly 4 million adults (1.6% of the population) have CLD [5]. The incidence of thrombocytopenia associated with CLD is higher in cirrhotic patients (64%) compared with noncirrhotic patients (5.5%) [6]. Thrombocytopenia in CLD is almost always linked to cirrhosis.

Treatment of thrombocytopenia in patients with CLD poses a substantial economic burden, with significant direct and indirect costs [7]. Direct costs include costs due to blood monitoring, hospital stays, therapy to increase platelet count, and complications of therapy and/or bleeding. Indirect costs include loss of work days, decreased quality of life, and a delay in medical procedures [7]. For instance, patients with CLD and thrombocytopenia can incur additional costs upward of $4800 for a normally uncomplicated procedure, such as a tooth extraction, compared with patients without thrombocytopenia [7]. In a retrospective analysis of patients with CLD, the mean overall healthcare costs for the 2.3%

of patients with both CLD and thrombocytopenia were 3.5 times higher than costs for patients without thrombocytopenia [8]. In addition, many patients do not receive needed procedures that would improve their survival or health-related quality of life due to low platelet counts.

Historically, treatments for CLD-associated thrombocytopenia included platelet transfusions, splenic artery embolization, and splenectomy. Most of these approaches are invasive and/or costly and often not appropriate for patients with CLD. New therapeutic options such as the use of TPO agonists are also now available and Food and Drug Administration (FDA) approved [1, 9, 10]. Effective management of thrombocytopenia will not only enable patients to get medically necessary procedures with a lower risk of bleeding complications, it will also likely reduce associated healthcare costs and improve patient outcomes [11].

This review outlines the current treatment options for thrombocytopenia in patients with CLD, explores their limitations, and proposes a revised treatment algorithm for the management of thrombocytopenia in this patient group.

Coagulation and Platelet Dysfunction in Chronic Liver Disease

Patients with CLD have lower levels of both procoagulant and anticoagulant factors and are at an increased risk of bleeding and, paradoxically, also at risk for thrombosis. In cirrhotic thrombocytopenia, a platelet dysfunction is also present in these patients. As a patient's liver disease worsens, the platelet defect also becomes progressive with an impact on platelet adhesion, activation, and aggregation. Compared to healthy controls, (1) there is a decrease in platelet adherence to the subendothelium, (2) there is less platelet aggregation in patients with cirrhosis accompanied by reduced transmembrane signaling, and (3) there is an inability to activate in response to appropriate stimuli [12].

Thrombocytopenia as a Common Complication in Patients with Chronic Liver Disease

Thrombocytopenia is a common hematological complication of cirrhosis, found in as many as 84% of patients [6]. The presence of thrombocytopenia in patients with liver disease is a useful noninvasive indicator of the development of portal hypertension caused by cirrhosis or severe liver fibrosis [6]. Changes in platelet levels in these patients can be a result of (1) reduced production of platelets (e.g., reduced TPO), (2) splenic sequestration of platelets (e.g., portal hypertension leading to hypersplenism with an inverse relation between the spleen size and platelet count), or (3) increased destruction of platelets/increased platelet consumption (e.g., immune-mediated destruction) (Fig. 1) [2, 13, 14].

For patients with CLD, thrombocytopenia and the risk of bleeding complications can cause delays or a cancelation of medically important invasive diagnostic and therapeutic procedures [11, 15]. Data on the overall significance of platelet counts in patients with cirrhosis are equivocal as several studies indicate severe thrombocytopenia to be a significant predictor of major bleeding and re-bleeding, while other studies show no correlation between platelet counts less than 50×10^9/L and an increased risk of periprocedural bleeding. Risk of potentially serious bleeding increased significantly in patients with platelet counts of $\leq 60{,}000/mm^3$ in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) study of patients with hepatitis C and advanced liver disease that underwent a liver biopsy [16]. A retrospective analysis based on a claims database of more than 56,000 patients showed that 27.8% of patients with CLD who had thrombocytopenia had a bleeding event, compared with 10% of patients with CLD without thrombocytopenia. The same was true with platelet transfusions; 8.1% of patients with CLD with thrombocytopenia received a platelet transfusion, compared with < 1% of patients with CLD without thrombocytopenia [8]. While there are some studies that found no increase in the risk of bleeding with platelet counts < 50,000–60,000/μL, doctors are still reluctant to perform some procedures until platelet levels reach near-normal levels in patients with CLD and associated thrombocytopenia [17].

Types of Elective Invasive Procedures in Patients with Chronic Liver Disease

Due to the nature of the disease, patients with CLD undergo numerous diagnostic and therapeutic procedures as part of their ongoing care or liver transplant evaluation (i.e., endoscopies, biopsies, ligations, percutaneous procedures). These procedures are associated with a range of bleeding risk from low to high, yet limited data on the safety of these procedures in patients with severe thrombocytopenia are available [15, 18].

Current Nonpharmacological Treatment Options for the Management of Thrombocytopenia in Patients with Chronic Liver Disease

Splenectomy

All patients with CLD and thrombocytopenia are considered suboptimal surgical candidates largely due to portal hypertension, which is associated with significant morbidity and mortality. Surgical complications of laparoscopic splenectomy include a substantial risk for complications, including portal and/or splenic vein thrombosis and hemorrhage. Open splenectomy includes a higher rate of those complications

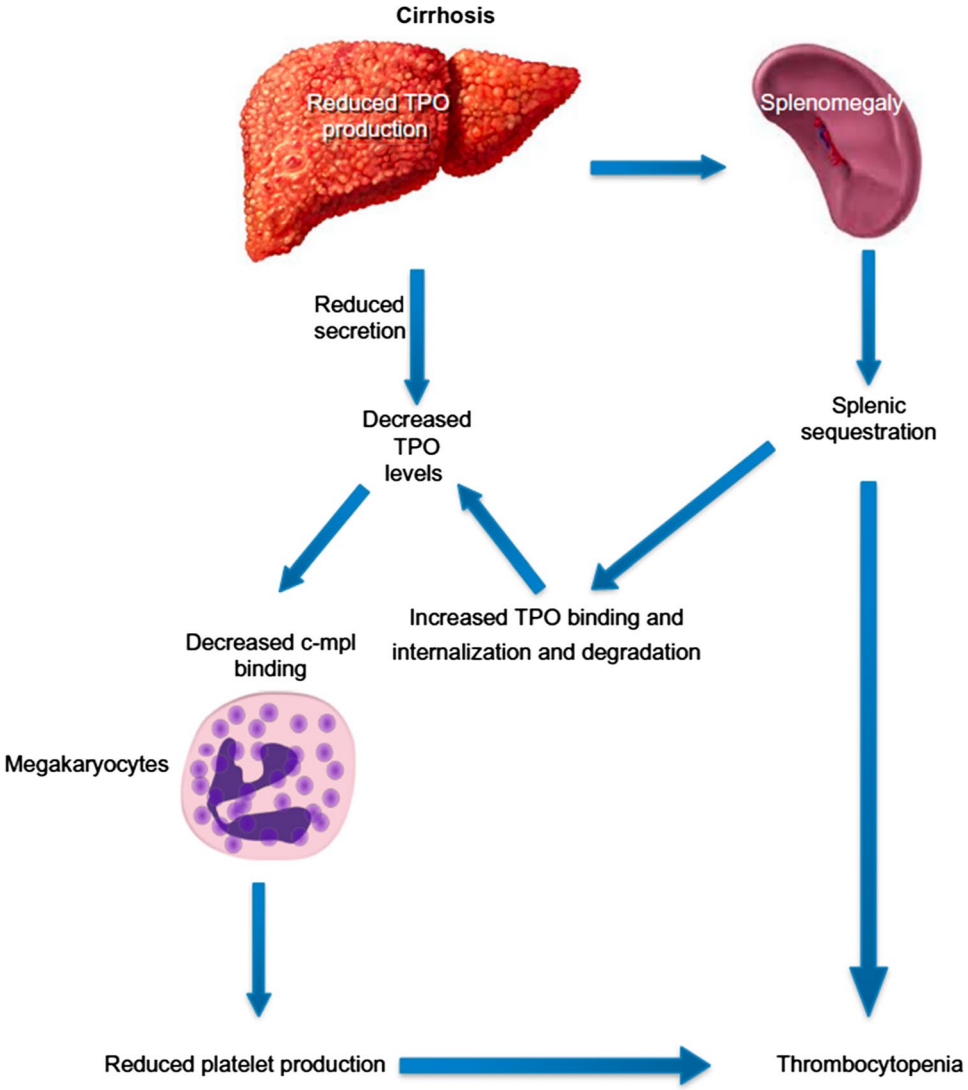

Fig. 1 Common causes of thrombocytopenia in patients with cirrhosis. Abbreviation: TPO, thrombopoietin [46]. Used with permission from RightsLink

in addition to infection and injury to the pancreatic tail [19, 20]. Currently, due to lack of supportive evidence and high complication rates, open splenectomy is not practiced or recommended, and the use of laparoscopic splenectomy is controversial and also associated with substantial morbidity in CLD patients [19].

Partial Splenic Arterial Embolization

In the past, partial splenic arterial embolization (PSAE) was used prophylactically to improve thrombocytopenia in patients with hepatitis C virus (HCV)-induced cirrhosis and hypersplenism to facilitate interferon-based antiviral therapy.

Advantages of PSAE over laparoscopic splenectomy include a decreased risk of sepsis and mortality [11, 19]. Complications of PSAE include pneumonia, peritonitis, splenic abscess, and portal vein thrombosis. Additionally, the procedure is invasive and has both significant cost and uncertain long-term benefit. In many patients with advanced liver disease, these limitations make PSAE an unsuitable option [11, 19].

Platelet Transfusion

Platelet transfusion has been the gold standard for thrombocytopenia treatment in CLD [11]. Despite advances in terms of platelet collection, storage, and transfusion, some risks, including infection, alloimmunization, febrile, and non-hemolytic reactions, are associated with platelet transfusion [11]. The most common complication is the development of refractoriness, which happens in about 50% of the patients, a result of human leukocyte antigen alloimmunization, and nonimmune platelet consumption associated with splenomegaly, disseminated intravascular coagulation (DIC), and septicemia [20]. New platelets are also sequestered in the

spleen, and this, along with the small number of platelets given, often leads to a suboptimal response in terms of both the magnitude and duration of platelet increases. Further, despite advances in preservation techniques, a major limitation of this treatment is the short shelf life of the platelet preparations, which must be used within 4 days to prevent bacterial growth [21].

Initiation of prophylactic platelet transfusion is often performed in thrombocytopenic patients at an increased risk of bleeding [22]. However, this may not be considered an option for patients with CLD-associated thrombocytopenia, as guidelines issued by various bodies, including the American Society of Clinical Oncology and the College of American Pathologists, do not discuss in detail the threshold for platelet transfusion before invasive procedures or surgery in this patient population [22]. The recommended platelet threshold values before invasive procedures or major surgery that have been published in the literature are greatly variable and often depend on the perceived risk of the procedure and the patient type [23, 24]. Yet, a threshold of a platelet count of 50,000/μL is generally used to determine whether prophylactic/therapeutic platelet transfusions should be initiated in patients with CLD, although this cutoff might be subjecting patients to unnecessary transfusions that provide no additional benefit [24].

To alleviate the problems associated with blood donation and its adverse effects, alternative transfusion sources, such as hematopoietic stem cells, independently developed human mesenchymal stromal cells, pluripotent embryonic stem cells, induced pluripotent stem cells, and preadipocytes, are being investigated [21]. However, these have shown little success so far, especially when it comes to generating larger quantities of the product [21].

Current Pharmacological Treatment Options for the Management of Thrombocytopenia in Patients with Chronic Liver Disease

Pharmacological therapies that provide effective treatment for thrombocytopenia in CLD target the biological pathway of thrombopoiesis. Factors that play a role in this process include TPO, stem cell factor (SCF), stromal cell-derived factor-1, interleukin-1 (IL-1), interleukin-3 (IL-3), interleukin-6 (IL-6), interleukin-11 (IL-11), granulocyte–macrophage colony-stimulating factor, leukemia inhibitory factor, and erythropoietin. The development of megakaryocytes from bone marrow stem cells is driven by these cytokines acting at different stages of thrombopoiesis: from stem cell to multipotent progenitor, committed megakaryocyte progenitor cell, immature megakaryocyte, mature megakaryocyte, and finally, platelets (Fig. 2). Unlike the other cytokines, TPO plays a central role at each stage of thrombopoiesis. Of the cytokines, SCF, IL-3, and IL-11 play a more significant role. IL-3 acts as a proliferation factor, while SCF and IL-11, along with TPO, increase the number and maturation of megakaryocyte precursors [25].

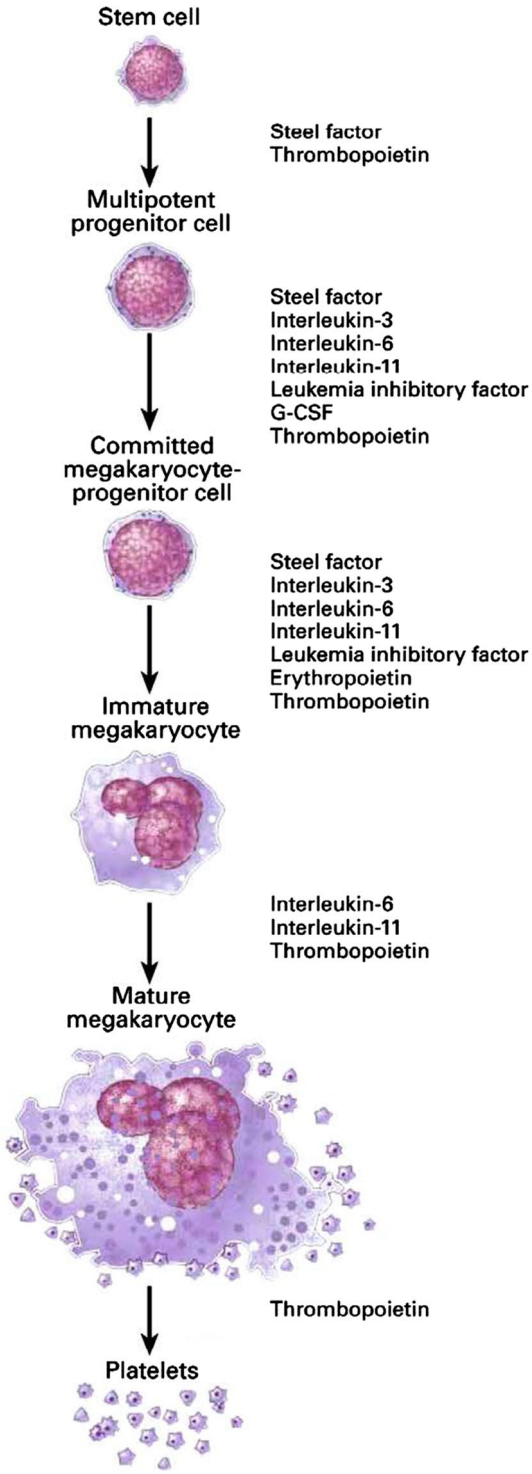

Fig. 2 Role of thrombopoietin in thrombopoiesis. Abbreviation G-CSF, granulocyte colony-stimulating factor [15]. Used and adapted with permission from RightsLink

TPO is synthesized primarily by hepatocytes, and circulating levels of TPO are regulated via a negative feedback loop [25]. Impaired liver function therefore decreases levels of TPO, leading to a reduction of platelet counts. Binding of the cytokines to their receptors on megakaryocyte precursors (e.g., TPO-R Mpl) activates signaling cascades that result in increased platelet production. Pharmacologic agents act in a similar manner by binding to and activating different receptors on the megakaryocyte precursor to stimulate platelet production [25].

Thrombopoietin Receptor Agonists

The early 2000s saw the emergence of pharmacologic TPO-R agonists that did not have homology to endogenous TPO and did not produce an antigenic effect. Activation of the c-Mpl receptor by TPO regulates megakaryocyte proliferation and differentiation into platelets. Agonists of c-Mpl receptor utilize this mechanism to increase platelet counts [26]. Currently, several c-Mpl agonists/mimetics, including romiplostim (Nplate), eltrombopag (Promacta), avatrombopag (Doptelet), and lusutrombopag (Mulpleta), are approved for clinical use in the treatment of thrombocytopenia (Fig. 3). Of these, only avatrombopag and lusutrombopag have been deemed safe and effective by the FDA to treat thrombocytopenia in adult patients with CLD who are scheduled to undergo a procedure and have been approved for that indication in the USA. Collated information about their route of administration, dose, half-life, and approved indications are listed in Table 1. Some of the advantages to TPO agonists are the fact that they have a long duration of platelet increase compared to platelet transfusion, can be used in patients who are poor surgical candidates, and do not have significant procedure-related complications, although there may be a risk of portal vein thrombosis with some of these agents [19].

Romiplostim

Romiplostim is a parenterally administered TPO-R agonist indicated for the treatment of thrombocytopenia in patients with chronic idiopathic thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy [27]. Romiplostim has four identical TPO agonist peptides with glycine bridges to connect them. It also contains an Fc carrier domain to increase its half-life. It has no sequence homology to endogenous TPO, and therefore, avoids the production of cross-reactive antibodies. Like TPO, it binds to the TPO-R-initiating signaling pathways [27]. A single-center, single-arm, open-label study in 35 Egyptian patients with CLD with severe thrombocytopenia secondary to HCV infection investigated the effect of preoperative romiplostim treatment (2 µg/kg once weekly). Ninety-four percent of the patients achieved the primary endpoint of two consecutive visits with a platelet count ≥ 70,000/µL [28]. All patients achieved a rapid response to treatment with a detectable increase in platelet counts between 1 to 1.5 weeks and a peak effect between 18 and 39 days [28]. The only reported adverse effect was headache with no bleeding or thromboembolic complications [28].

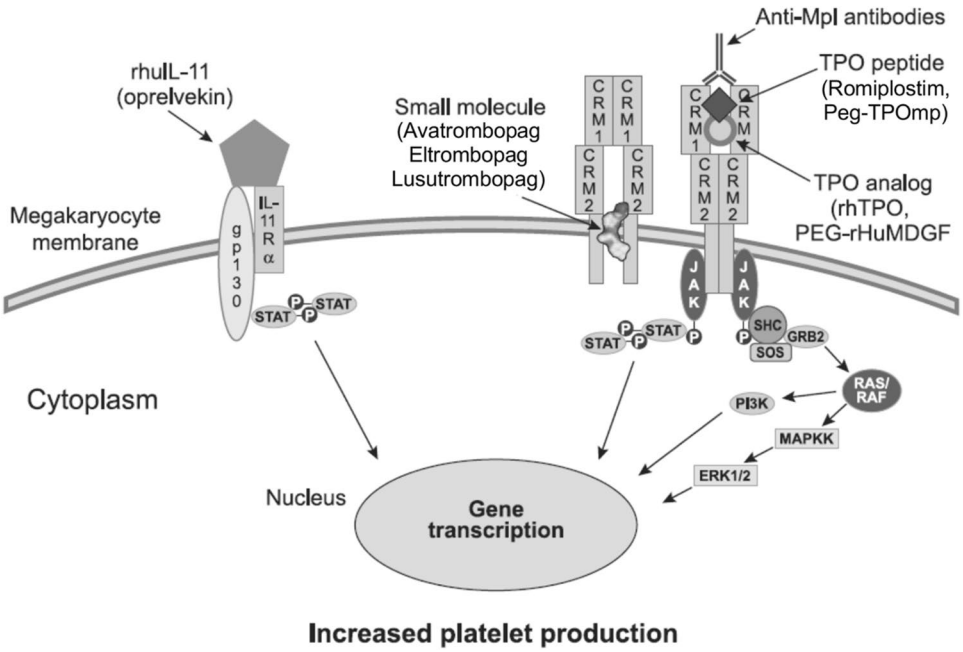

Fig. 3 Mechanism of action of platelet-centric thrombopoietic agents. Abbreviations: IL-1, interleukin 11; rhTPO, recombinant human thrombopoietin; rHuIL-11, recombinant human interleukin 11; and TPO, thrombopoietin [25]. Used and adapted with permission from RightsLink

Table 1 TPO-RA treatment options for thrombocytopenia in patients with chronic liver disease

Compound	Dose and route of administration	Pharmaco-kinetics data ($T_{1/2}$ in Hours)	Status/indication	Peri-/preprocedural adjustment	Laboratory monitoring
Romiplostim	1–10 µg/kg QW	84	Approved in the United States and Europe for use in adult patients with:	No guidance on peri-/preoperative management/adjustment	CBC with differential + platelet count
	Subcutaneous		Treatment-refractory chronic ITP		
Eltrombopag (small-molecule platelet growth factor)	25–75 mg QD (ITP)	21–32 (healthy)	Approved for use in patients with:	No guidance on peri-/preoperative management/adjustment	CBC with differential + platelet counts
	25–100 mg QD (HCV)	26–35 (ITP)	Treatment-refractory chronic ITP or SAA		Clinical hematology and liver tests (serum ALT, AST, bilirubin)
	50–150 mg		TCP with chronic HCV infections		
	QD (SAA)				
	Oral				
Avatrombopag (small-molecule TPO agonist)	40–60 mg once daily	19	Approved in the USA for use in patients for:	Begin avatrombopag 10 to 13 days prior to the scheduled procedure	Obtain a platelet count prior to the administration of avatrombopag therapy and on the day of a procedure
	Oral		Treatment of TCP associated with liver disease prior to an elective procedure	Patients should undergo procedure 5 to 8 days after the last avatrombopag dose	
Lusutrombopag	3 mg once daily for 7 days	27 (healthy)	Approved in the USA for use in patients for:	Begin lusutrombopag 8 to 14 days prior to the scheduled procedure	Platelet count at baseline before initiation and again no more than 2 days prior to procedure
	Oral		Treatment of TCP associated with CLD in patients who are scheduled to undergo a medical or dental procedure	Patients should undergo procedure 2 to 8 days after the last lusutrombopag dose	

CBC complete blood count; *CLD* chronic liver disease; *HCV* hepatitis C virus; *ITP* idiopathic thrombocytopenia; *QD* once a day; *QW* once a week; *SAA* severe aplastic anemia; $T_{1/2}$ half-life; *TCP* thrombocytopenia; *TPO* thrombopoietin

Eltrombopag

Eltrombopag interacts with the transmembrane domain of the TPO-R on megakaryocyte precursors and megakaryocytes, inducing their proliferation and differentiation to increase platelet production. An advantage of eltrombopag over romiplostim is that it can be orally administered. Eltrombopag is approved for the treatment of chronic immune ITP in adults and patients > 1 year of age who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy, and also in adults with chronic hepatis C to allow initiation and maintenance of antiviral therapy [29]. The boxed warning for eltrombopag lists the risk of hepatic decompensation in patients with chronic hepatis C as well as the risk of hepatotoxicity [29].

Two pivotal multicenter, randomized trials, the Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C-Related Liver Disease (ENABLE)-1 and ENABLE-2 trials, were able to demonstrate the ability of eltrombopag to increase platelet counts in patients with hepatitis C, thereby enabling them to maintain interferon-based antiviral treatments [30]. Platelet counts generally increased within 1 to 2 weeks after initiation and decreased within 1 to 2 weeks after discontinuation. Eltrombopag administered prior to elective invasive procedures reduced the requirement for platelet transfusion in patients with CLD compared with placebo; the platelet transfusion frequencies were 28% and 81%, respectively [31]. However, the study had to be terminated because of an increased incidence of portal vein thrombosis possibly associated with increases in platelet count to > 200,000 per cubic millimeter [31]. Of the six patients in the eltrombopag-treated group who had portal vein thrombosis, five had platelet counts that were > 200,000 per cubic millimeter [31]. As such, eltrombopag is not recommended as an alternative to platelet transfusions in patients with CLD-associated thrombocytopenia undergoing an elective invasive procedure [31].

Avatrombopag

Avatrombopag, like eltrombopag, is an oral drug that binds to the TPO-R, inducing a cascade of cellular events leading to increased platelet production [32]. Unlike eltrombopag, it is currently indicated for the treatment of thrombocytopenia in patients with CLD who are scheduled for a medical procedure. Two international, identically designed, randomized, double-blind, placebo-controlled phase 3 trials, ADAPT-1 ($n = 231$) and ADAPT-2 ($n = 204$), found avatrombopag superior to placebo in reducing the need for platelet transfusions or medical rescue procedures for bleeding in patients with thrombocytopenia and CLD undergoing a scheduled procedure [33]. Patients were stratified based on a lower baseline (< 40,000/μl) or higher baseline (≥ 40,000/μl–< 50,000/μl) platelet count cohort. Patients in the low-baseline platelet cohort received avatrombopag 60 mg or placebo once daily for 5 days, and the high-baseline cohort received avatrombopag 40 mg or placebo once daily for 5 days [32, 33]. Patients underwent a broad spectrum of scheduled procedures, which ranged from low- to high-bleeding risk. Responders were defined as the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization up to 7 days postprocedure. In both baseline platelet count cohorts (and in both trials), patients in the avatrombopag group had a significantly greater proportion of responders than the corresponding placebo treatment groups. In the low-baseline cohort group of ADAPT-1, 66% of patients in the avatrombopag group were responders compared with 23% in the placebo group, while in ADAPT-2, the corresponding numbers were 69% and 35%, respectively. In the high-baseline cohort group of ADAPT-1, 88% of patients in the avatrombopag group were responders compared with 38% in the placebo group, while in ADAPT-2, the corresponding numbers were 88% and 33%, respectively [32, 33]. In general, platelet counts increased with a peak effect between 10 and 13 days and returned to baseline by day 35. The overall safety profile was similar for avatrombopag and placebo with hyponatremia reported as the most common serious adverse event. One avatrombopag TEAE (asymptomatic portal vein thrombosis) was reported in the high-baseline platelet cohort and identified as nonserious and possibly related. Physicians are asked to monitor for thromboembolic complications in patients with CLD as TPO-R agonists may be associated with thrombotic and thromboembolic complications in patients with CLD [32].

Lusutrombopag

The latest TPO-R agonist to get FDA approval is lusutrombopag (July 2018), which is also an orally administered agent indicated for the treatment of thrombocytopenia in adult patients with CLD who are scheduled to undergo a procedure [34]. Safety and efficacy of lusutrombopag were evaluated in two randomized, double-blind, placebo-controlled trials: the Lusutrombopag for Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS)-1 ($n = 97$) and L-PLUS-2 ($n = 215$). In L-PLUS-1, 78% of patients who received lusutrombopag required no platelet transfusion prior to the procedure, compared with 13% of patients who received placebo [34, 35]. The comparable percentages for patients who received lusutrombopag and patients who received placebo in the L-PLUS-2 trial were 65% and 29%, respectively. Mean platelet counts increased in correlation to the AUC across the studied dose ranges, and the median time to reach peak effect with the 3-mg dose was 12 days. The most common

adverse effect reported was headache, while the most common serious adverse reaction was portal vein thrombosis, though the rate did not differ between drug-treated and placebo-treated patients [34]. In the L-PLUS-1 trial, one patient each in the lusutrombopag and placebo treatment groups had a thrombotic event, although neither was associated with a platelet count ≥ 200,000/µl. The patient in the lusutrombopag had severe portal vein thrombosis 14 days after surgery that was probably related to the study drug. The platelet count in this patient was 79,000/µl [36]. Two thrombotic TEAEs each in the lusutrombopag and placebo groups were reported in the L-PLUS-2 trial. All were asymptomatic and found during protocol-defined imaging [37]. Similar to other TPO-R agonists, when physicians prescribe lusutrombopag, they are asked to monitor for thromboembolic complications in patients with CLD, as TPO-R agonists may be associated with thrombotic and thromboembolic complications in patients with CLD [34].

TPO-R Agonists and the Risk of Portal Vein Thrombosis in Patients with Chronic Liver Disease and Thrombocytopenia

A recent meta-analysis of four studies including 1953 patients that compared the effect of three TPO-R agonists (eltrombopag, avatrombopag, and lusutrombopag) and placebo in patients with CLD and thrombocytopenia observed a trend toward increased risk of portal vein thrombosis following treatment with the TPO-R agonists (1.6% overall for the TPO-R agonists and 0.6% for placebo); however, this difference was not statistically significant. Interestingly, the meta-analysis revealed a significant association between portal vein thrombosis and treatment with eltrombopag alone, but not with avatrombopag and lusutrombopag treatments.

A further analysis of three studies including 514 patients to study the effect of TPO-R agonists (eltrombopag, avatrombopag, and lusutrombopag) versus placebo on portal vein thrombosis in patients with chronic liver disease and thrombocytopenia who were undergoing an elective procedure also showed a similar trend toward increased portal vein thrombosis (2.8% vs. 0.9%, respectively) in patients treated with the TPO-R agonists; again this difference was not statistically significant.

Finally, the authors analyzed the incidence of arterial and venous thromboembolic events in two studies that included 1727 patients treated with either eltrombopag or placebo. The incidence of thromboembolic events was 3.6% and 1.1% in patients treated with eltrombopag and placebo, respectively, and this difference was statistically significant [38].

The meta-analysis reveals that overall, the TPO-R agonists do not increase the risk of portal vein thrombosis in patients with chronic liver disease and thrombocytopenia. However, taken individually, there are differences between the TPO-R agonists in terms of thrombotic risk, with eltrombopag carrying a significant thrombotic risk [38].

Treatment Algorithm for the Management of Thrombocytopenia in Patients with Chronic Liver Disease Based on the Listed Treatment Options

The management of thrombocytopenia in patients with CLD is a challenge for physicians. In the past, splenectomy and partial splenic embolization were the popular choices for management because of the durability of increased platelet counts with these procedures. However, all patients with CLD and thrombocytopenia are poor candidates for surgery and given the high morbidity and mortality rates, the use of these procedures in this patient cohort is controversial. More recently, TPO stimulators are being utilized for the treatment of thrombocytopenia in patients with CLD. Unlike the past, physicians now have access to a larger variety of pharmacological options to treat patients with CLD. These include eltrombopag and romiplostim that have had approval for other indications for several years, but also the newer TPO-R agonists, avatrombopag and lusutrombopag, both of which have proven efficacy and are indicated for treatment in patients with CLD. As with all TPO-R agonists, however, there is a potential risk of thromboembolism that must be monitored [19].

In light of the new choices available, we propose a treatment algorithm (Fig. 4) that is a modified version of one developed by Gangireddy et al. for the management of mild, moderate, and severe thrombocytopenia in patients with advanced liver disease. As in the original algorithm, we advocate periodic blood monitoring without any treatment for mild thrombocytopenia [19]. For moderate and severe thrombocytopenia, we recommend the use of TPO-R agonists(s) as the first choice with platelet transfusions only in cases of major surgical procedures with a high risk of bleeding, such as neurological procedures, or in cases of intracranial bleeding, or DIC, in order to bring the platelet levels over 100,000/µL. In case of multiple transfusions, or in case the TPO-R agonist(s) fail(s) to work adequately, a surgical or interventional radiologic treatment may be an option as a last resort if the patient is deemed fit [19].

The choice of treatment also depends on the underlying cause of thrombocytopenia. For thrombocytopenia caused by platelet sequestration in the spleen, PSAE or laparoscopic splenectomy can be effective in cirrhotic patients. The choice between the two treatments is based on splenic volume, intention of the treatment (the extent to which an increase in platelet counts is required), and the patient condition (e.g., if general anesthesia is available). These therapies should likely be limited to situations where a prolonged duration of increased platelets is needed (e.g., recurrent bleeding), or a contraindication to TPO agonists is present [39]. On the

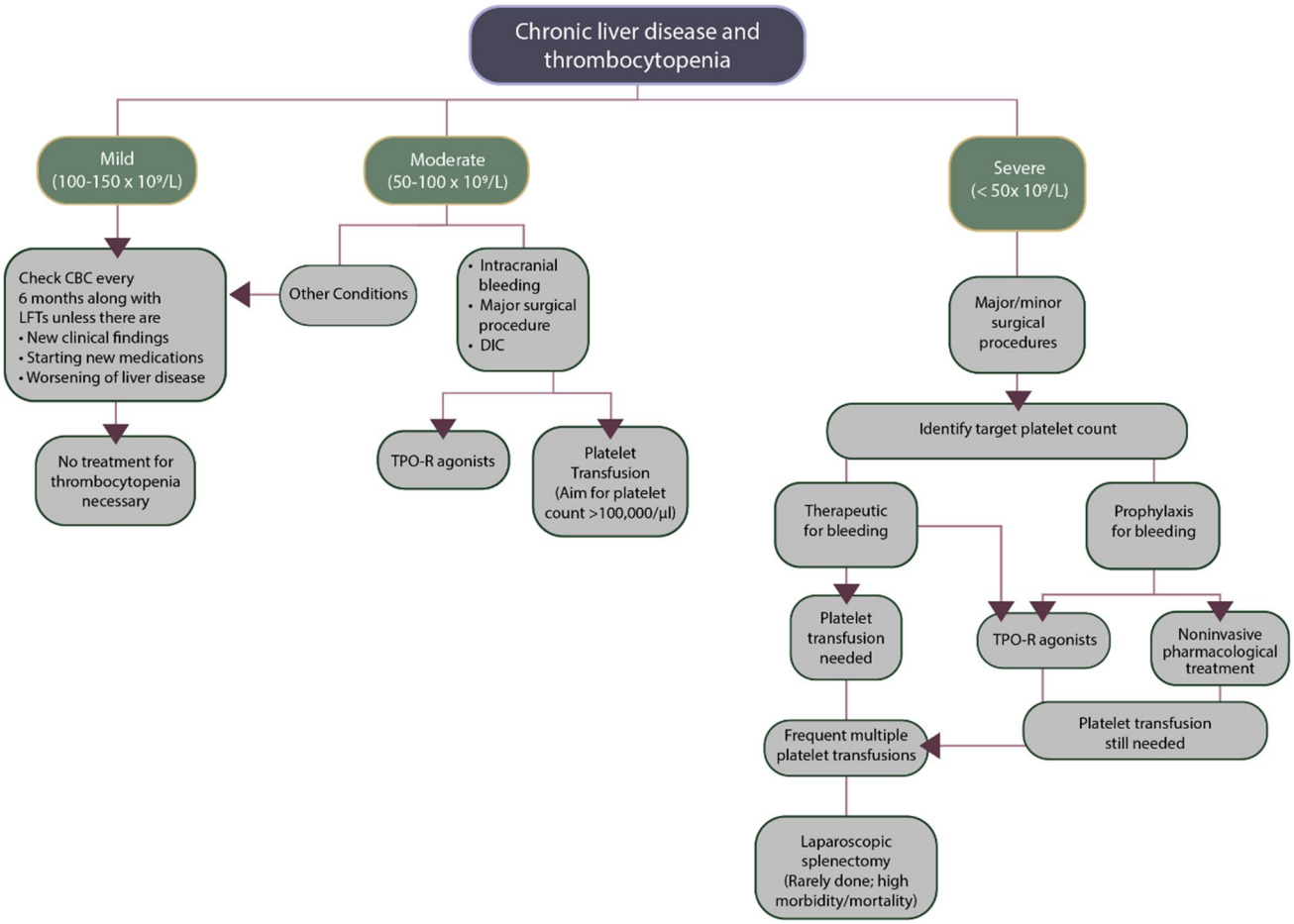

Fig. 4 Management of mild, moderate, and severe thrombocytopenia in patients with chronic liver disease. Abbreviations: CBC, complete blood count; DIC, disseminated intravascular coagulation; HCV, hepatitis C virus; LFT, liver function test; PSE, partial splenic embolization; and TPO-R, thrombopoietin receptor. Adapted and modified from: Gangireddy et al. [19]

other hand, thrombocytopenia is also caused by a decreased production of TPO and can be treated with far less morbidity using TPO agonists and other noninvasive pharmacological treatments (e.g., RFA) [9].

Limitations in the Current Treatment Algorithm

An ideal treatment therapy for thrombocytopenia in CLD should be effective in a majority of patients, orally bioavailable, active across various disease states, relatively free of adverse effects, and cost-effective [11]. No therapeutic option currently has been demonstrated to meet all these requirements, but the new oral TPO-R agonists have been a step forward as the first safe and effective FDA-approved therapy for thrombocytopenia in CLD.

Platelet transfusions, the backbone of thrombocytopenia treatment, lack appropriate guidelines based on empirical data to help the physician decide on a treatment plan that would provide the most optimal response in patients with liver cirrhosis. While there are some organizations that have provided position statements on utilizing platelet transfusions in particular procedures (Table 2), the relevance of these recommendations for patients with liver cirrhosis is unclear [22, 40–42]. Similarly, there is no consensus on the appropriate threshold values for prophylactic transfusions in patients with CLD. In any case, platelet transfusions are inappropriate as a long-term management option in patients with CLD, mainly due to the risk of alloimmunization, which can increase the risk of rejection if a liver transplantation is required in the future [43].

The new TPO-R agonists, avatrombopag and lusutrombopag, while satisfying several of the requirements of an ideal therapeutic agent, are associated with potential serious adverse events like portal vein thrombosis in patients with CLD. However, recent studies strongly support a positive benefit–risk profile of TPO-R agonists, and these are likely the treatments of choice for the majority of patients with CLD and thrombocytopenia [33, 35].

Table 2 Platelet transfusion recommendations

Society	Year	Platelet transfusion
American Association of Study of Liver Diseases (AASLD)	2009	Platelet transfusion should be considered when levels are <50 to 60×10^9/L. (This applies whether one is attempting a transcutaneous or transvenous biopsy)
American Society of Gastrointestinal Endoscopy (ASGE)	2012	Platelet threshold 20×10^9/L for diagnostic endoscopy; 50×10^9/L if biopsies performed
Society of Interventional Radiology (SIR)	2012	Platelet transfusion should be recommended for platelet counts $<50\times10^9$/L (low, moderate, and severe risk of bleeding)

New Treatments in Development

There are several TPO mimetics in various stages of development, including the peptide TPO mimetic Peg-TPOmp (J&J) in phase I trials, nonpeptide TPO mimetic totrombopag (SB-559448; LGD-4665; GSK and Ligand) currently in phase II trials, and nonpeptide TPO mimetic butyramide (Shionogi) in phase I trials. Other agents in preclinical stages of development include monoclonal antibodies that can bind and activate TPO-Rs [44]. Of these, VB22B sc (Fv)2 is a promising candidate comprised of a dimerized part of the Fab region, which was found to dramatically increase the agonist activity in a TPO-dependent cell proliferation assay [44, 45].

Conclusions

Patients with CLD tend to have various hematologic and coagulation abnormalities. There is a difficult balance of hemostasis in these patients, which may be tipped toward bleeding or thrombosis, depending on various factors. Thrombocytopenia is common in patients with CLD and is often a predictor for bleeding from medical procedures. However, data on the overall significance of platelet counts in patients with cirrhosis are equivocal as several studies indicate severe thrombocytopenia to be a significant predictor of major bleeding and re-bleeding, while other studies show no correlation between platelet counts less than 50×10^9/L and increased risk of periprocedural bleeding. Although the management of thrombocytopenia in patients with CLD is a challenge, our recommendations and suggested treatment algorithm recognize there are many treatment options available to treat thrombocytopenia in patients with CLD. However, it is important to emphasize that patients should be evaluated based on the underlying cause of thrombocytopenia, the type of procedure being conducted, and the risk of bleeding. In our proposed treatment algorithm (modified version of one developed by Gangireddy et al.), we still advocate periodic blood monitoring without any treatment for mild thrombocytopenia, and for moderate and severe thrombocytopenia, we recommend the use of TPO-R agonists(s) as the first choice. There are a number of TPO-R agonists currently available, and more are in various stages of development to manage thrombocytopenia in patients with CLD who have to undergo various procedures. They have the advantages of oral availability, outpatient dosing, and lesser complications in the periprocedural management of thrombocytopenia as compared with platelet transfusions. As long as the rates of adverse thrombotic events in patients remain manageable, TPO-R agonists are likely to gain acceptance and dominate the field of thrombocytopenia treatment choices in patients with CLD.

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Author's contribution SS and RSB were involved in study concept and design; they contributed to acquisition of data; they analyzed and interpreted the data; they contributed to critical revision of the manuscript for important intellectual content; they contributed to statistical analysis (not applicable), provided administrative, technical, or material support, and supervised the study. SS, RSB and BioCentric, Inc., drafted the manuscript.

Compliance with ethical standards

Conflict of interest The authors of this manuscript have no conflicts of interest to disclose.

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