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REVIEWS

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Thrombocytopenia in chronic liver disease

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Abstract

Thrombocytopenia is a common haematological disorder in patients with chronic liver disease. It is multifactorial and severity of liver disease is the most influential factor. As a result of the increased risk of bleeding, thrombocytopenia may impact upon medical procedures, such as surgery or liver biopsy. The pathophysiology of thrombocytopenia in chronic liver disease has long been associated with the hypothesis of hypersplenism, where portal hypertension causes pooling and sequestration of all corpuscular elements of the blood, predominantly thrombocytes, in the enlarged and congested spleen. Other mechanisms of importance include bone marrow suppression by toxic substances, such as alcohol or viral infection, and immunological removal of platelets from the circulation. However, insufficient platelet recovery after relief of portal hypertension by shunt procedures or minor and transient recovery after splenic artery embolization have caused many to question the importance and relative contribution of this mechanism to thrombocytopenia. The discovery of the cytokine thrombopoietin has led to the elucidation of a central mechanism. Thrombopoietin is predominantly produced by the liver and is reduced when liver cell mass is severely damaged. This leads to reduced thrombopoiesis in the bone marrow and consequently to thrombocytopenia in the peripheral blood of patients with advanced-stage liver disease. Restoration of adequate thrombopoietin production post-liver transplantation leads to prompt restoration of platelet production. A number of new treatments that substitute thrombopoietin activity are available or in development.

KEYWORDS
chronic liver disease, cirrhosis, thrombocytopenia, thrombopoietin

1 | INTRODUCTION – EPIDEMIOLOGY OF THROMBOCYTOPENIA IN CHRONIC LIVER DISEASE

Thrombocytopenia is a common haematological complication in patients with chronic liver disease (CLD), and is generally defined as any decrease in platelet count below the lower normal limit (<150 000/μL, with subdefinitions 50-100 000/μL [moderate] and <50 000/μL [severe]).[1,2] A systematic literature review to assess the prevalence of thrombocytopenia found that definitions vary between studies and are based either on platelet counts, with threshold levels between ≤100 000/μL and ≤180 000/μL, or on criteria set in haematological guidelines.[3] In addition, the threshold is often operatively considered as the level below which performing invasive manoeuvres (e.g. liver biopsy) or administering interferon (IFN) therapy could be regarded as dangerous (i.e. <50-75 000/μL).[4-6]

The prevalence of thrombocytopenia varies according to a number of factors, such as the definition used, the patient population and severity of underlying liver disease, and the degree of thrombocytopenia

Abbreviations: AE, adverse event; CLD, chronic liver disease; HCV, hepatitis C virus; HLT, heterotopic liver transplantation; IL, interleukin; ITP, immune thrombocytopenia; OLT, orthotopic liver transplantation; PEG-IFN, pegylated interferon; PEG-rHuMGDF, pegylated human recombinant megakaryocyte growth and development factor; QD, once daily; QW, once weekly; RFA, radiofrequency ablation; rhIL-11, recombinant human IL-11; rhTPO, recombinant human TPO; SAA, severe aplastic anaemia; TIPS, transjugular intrahepatic portosystemic shunt; TPO, thrombopoietin.

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is a useful early prognostic marker in cirrhotic patients.[7] The prevalence of thrombocytopenia in patients with chronic hepatitis has been reported to be only 6%, but occurs in up to 78% of patients with cirrhosis.[8-11] Moderate thrombocytopenia and severe thrombocytopenia are observed in approximately 13% and 1%, respectively, of cirrhotic patients,[2] but are dependent upon the stage of cirrhosis. Thus, the majority of thrombocytopenia cases are mild to moderate in severity. Patients with a count >50 000/μL are rarely symptomatic and clinically significant spontaneous bleeding does not usually occur until the platelet count is <10-20 000/μL.[12] Patients with stable liver disease are only at increased risk of bleeding if the thrombocytopenia is severe[13] or they are undergoing major surgery.[14] In patients with compensated cirrhosis, thrombocytopenia (defined as a platelet count <150 000/μL) was shown to be the most common peripheral blood alteration, occurring in almost 78%, while anaemia and leucopenia were much less frequent.[11]

This review focuses on the causes of thrombocytopenia in CLD, in particular the role of thrombopoietin (TPO) and the pharmacological treatment options using the TPO pathway that are available or under investigation.

Key points

- The limitations and possible risks associated with platelet transfusion (and other management strategies, e.g. splenic artery embolization, transjugular intrahepatic portosystemic shunts and splenectomy) have been well documented.
- The discovery of the cytokine thrombopoietin has led to the elucidation of a central mechanism of thrombocytopenia in chronic liver disease.
- Restoration of adequate thrombopoietin production post-liver transplantation leads to prompt restoration of platelet production.
- New treatments that substitute thrombopoietin activity are available or in development.
- The main indication for thrombopoietin agonists in patients with liver disease will be the peri-interventional management of thrombocytopenia.

2 | RISK OF THROMBOCYTOPENIA WITH PROCEDURES

2.1 | Invasive procedures

The prevalence of thrombocytopenia and incidence of procedure-related bleeding were investigated in 121 patients with cirrhosis during evaluation for orthotopic liver transplantation.[15] The prevalence of thrombocytopenia (platelets ≤150 000/μL) and severe thrombocytopenia (platelets ≤75 000/μL) were high: 84% and 51% respectively. In the 50 patients who underwent invasive procedures (endoscopic variceal ligation, transcatheter arterial chemoembolization, transjugular intrahepatic portosystemic shunt, dental extractions, large volume paracentesis, endoscopic polypectomy, radiofrequency thermal ablation, endoscopic gastric, thyroid and liver biopsies), there was a correlation between bleeding episodes and low platelet count, with bleeding in 31% of the 32 patients with a platelet count <75 000/μL, but no bleeding in the 18 patients with moderate thrombocytopenia. Significant coagulopathy (international normalized ratio >1.5) did not appear to be associated with bleeding. In another study, Indian patients with cirrhosis (n=380) were assessed prospectively according to the presence or absence of abnormal coagulation parameters (defined as INR ≥1.5 and/or platelet count ≤50 000/μL). These deranged conventional coagulation parameters did not predict clinically significant bleeding in cirrhosis and both high- and low-risk invasive procedures were carried out safely.[16]

Therapeutic procedures (but not diagnostic procedures with lower gauge needles) in cirrhotic patients may lead to mild bleeding complications, which are dependent upon the characteristics of the patient (e.g. higher risk with platelet count [≤50 000/μL], Child–Pugh stage C and alcoholic cirrhosis) and of the procedure itself.[17] Even the risk of bleeding events with liver biopsy is lower than commonly perceived. A subanalysis of 2740 liver biopsies from the HALT-C trial found only 16 bleeding events (0.6%).[18] The main risk factor for bleeding was platelet count ≤60 000/μL (5% rate), with virtually no risk >150 000/μL and very little risk >60 000/μL.

2.2 | Antiviral therapy

Thrombocytopenia has a major impact on patient care. Many physicians do not initiate interferon-based hepatitis C virus (HCV) antiviral therapy if platelet counts are low. Indeed, treatment guidelines suggest that patients with severe thrombocytopenia should not receive pegylated interferon (PEG-IFN)-based antiviral therapy[19] and it should be discontinued for platelet counts <25 000/μL or the dose reduced for counts <50 000/μL.[20] It has been suggested that thrombocytopenia represents an obstacle to initiation of PEG-IFN therapy in up to 6.5% of eligible patients with chronic HCV infection, and may be responsible for PEG-IFN dose reduction in up to ~20% of patients with pre-treatment low platelet count, thus potentially jeopardizing the outcome of antiviral treatment.[21-23] However, a review of clinical trials of PEG-IFN[24] found that only 4% of dose reductions were attributable to thrombocytopenia (20% due to neutropenia and 1% to anaemia). This issue is no longer of major concern in industrialized countries, where Peg-IFN-based therapies have been replaced by oral therapies that do not cause thrombocytopenia. However, it is important to consider thrombocytopenia in patients in other parts of the world, where PEG-IFN based therapies are still in use.

There is no evidence to support these thresholds for decreasing and discontinuing PEG-IFN-based therapy. Research suggests that PEG-IFN treatment is safe in patients with platelets >20 000/μL. In a single-centre cohort study involving 321 patients (n=68 with cirrhosis) receiving PEG-IFN-α and ribavirin treatment for HCV infection, bleeding episodes started at platelet counts of 20 000-40 000/

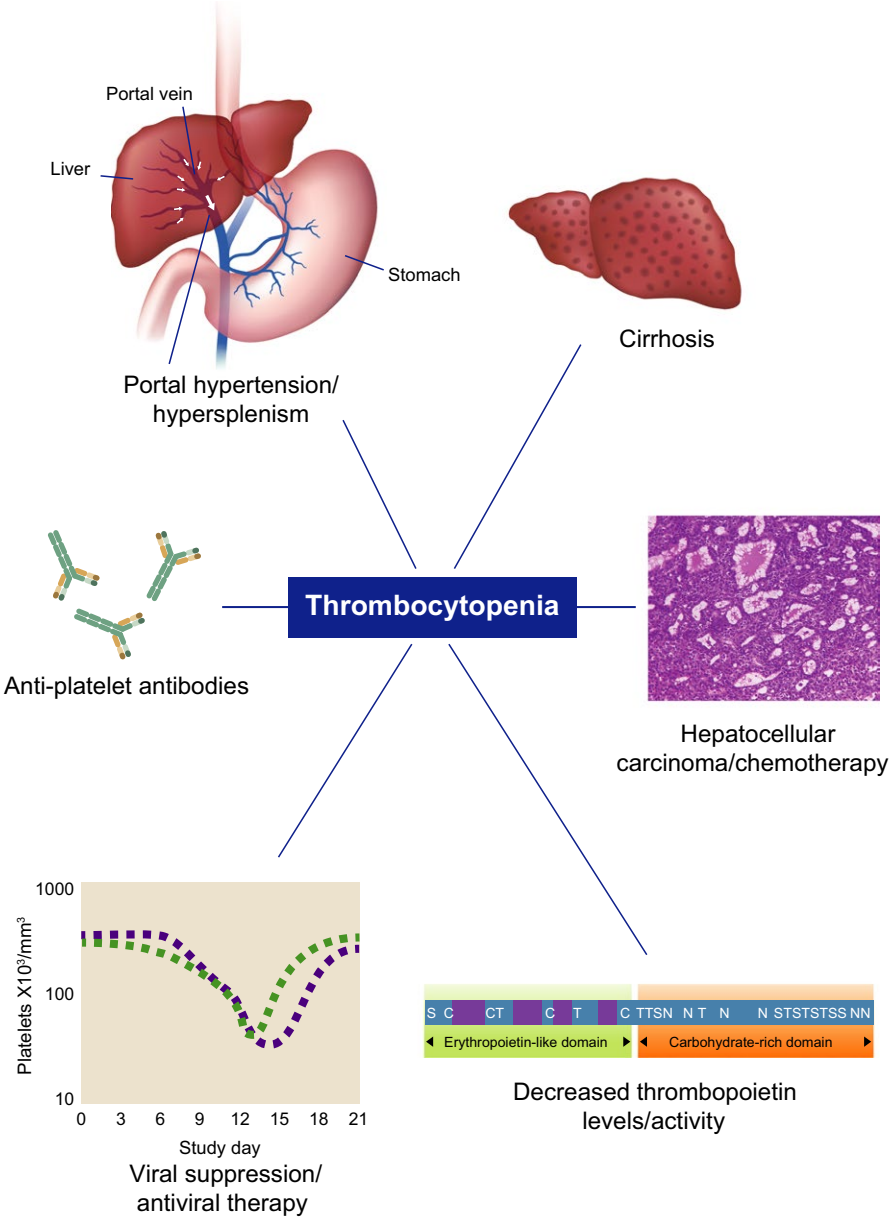


FIGURE 1 Multiple mechanisms that can lead to thrombocytopenia in patients with CLD.[2] Republished with permission of the Journal of Hepatology: the Journal of the European Association for the Study of the Liver, Elsevier BV, from Thrombocytopenia associated with chronic liver disease, Afdhal N, McHutchison J, Brown R, et al., 48 (6), 1000-1007. Copyright ©2008; permission conveyed through Copyright Clearance Center, Inc. [Colour figure can be viewed at wileyonlinelibrary.com]

μL. Most of the episodes were mild (primarily epistaxis or gingival bleeding), with only one severe episode, which was not related to thrombocytopenia.[25]

3 | CAUSES OF THROMBOCYTOPENIA IN CLD

Thrombocytopenia in CLD is always linked to cirrhosis, except in a few cases of HCV infection. Multiple pathophysiological mechanisms are responsible and more than one mechanism at a time may account for decreased platelet counts. Decreased levels/activity of the haematopoietic growth factor TPO, hepatic carcinoma, chemotherapy, bone marrow inhibition by excessive alcohol ingestion, hypersplenism secondary to portal hypertension, antiplatelet antibodies and antiviral treatment-induced myelosuppression may all contribute to the development of thrombocytopenia in CLD (Figure 1).[2] The major mechanisms for thrombocytopenia in cirrhosis are decreased production of TPO in the liver and splenic platelet sequestration.

3.1 | Thrombopoietin expression and hepatic production

Recent research efforts have led to the identification and characterization of molecules that play a key role in the regulation of thrombopoiesis. There are several important regulators of platelet production, including interleukin (IL)-3, -6 and -11 and steel factor, but TPO is the dominant thrombopoietic hormone (Figure 2). TPO is primarily produced by hepatocytes[26-28] and consists of two domains – an amino terminal and a carboxyl terminal. The amino-terminal shares homology with erythropoietin and binds to the c-Mpl receptor on the surface of megakaryocytes, megakaryocyte progenitor cells, platelets and stem

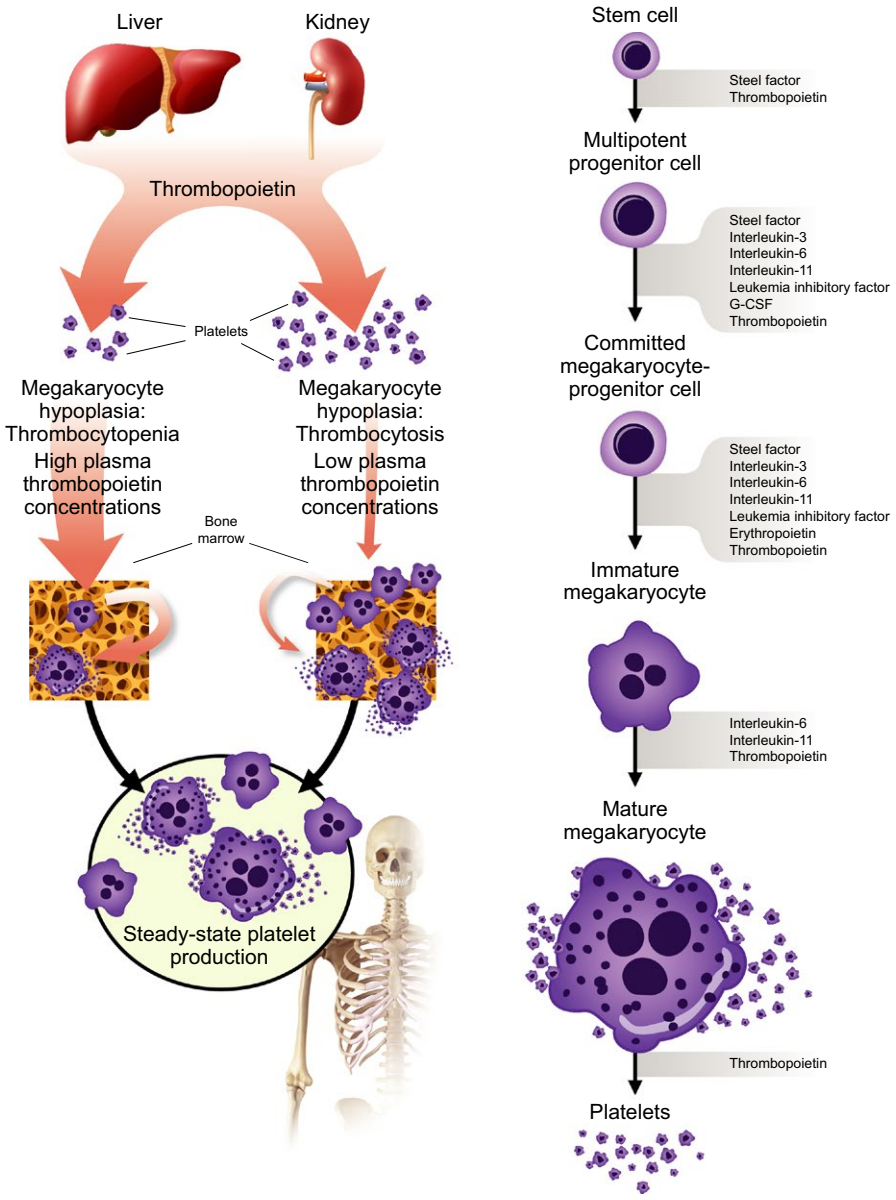


FIGURE 2 Role of thrombopoietin in megakaryopoiesis and thrombopoiesis.[29] From the New England Journal of Medicine, Kaushansky K, Thrombopoietin, 339, 746-754. Copyright ©1998 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [Colour figure can be viewed at wileyonlinelibrary.com]

cells.[29] The carboxyl terminal is responsible for the circulatory half-life of the hormone, as well as for aiding polypeptide folding.[29] TPO acts at all stages of thrombopoiesis and synergizes with other cytokines to stimulate both megakaryocytopoiesis and thrombopoiesis as well as platelet release into the circulation (Figure 2).[29,30]

TPO is produced by the liver in humans, whereas the kidneys also contribute in part in animals.[26,31] TPO is produced at a constant rate, irrespective of platelet count. There is no post-transcriptional or translational regulation of TPO production. TPO levels in peripheral blood are regulated through removal by binding to TPO receptors on platelets and megakaryocytes, which leads to increased TPO levels, with reduced platelets and megakaryocytes. As a consequence, TPO levels rise dramatically in liver-healthy patients with chemotherapy-induced thrombocytopenia, while TPO levels remain normal and, therefore, much too low in cirrhosis-associated thrombocytopenia (a state of TPO deficiency). Experimental evidence from animal studies shows that the amount of TPO produced in the liver and the peripheral platelet count are dependent upon the functional liver cell mass[32] and explain the TPO deficiency in severe liver damage.

Animal experiments showed a clear dose–response relationship between TPO or its receptor c-Mpl and peripheral platelet counts when TPO or the c-Mpl receptor had been "knocked-out" by homologous recombination.[33-35] In addition, megakaryocyte and peripheral platelet masses were reduced by >80%. Other knock-out studies found that the liver contributed 60% of the TPO required for maintenance of normal platelet count in mice, which could be reversed by transplantation of a wild-type liver.[36]

3.2 | TPO and CLD

Although TPO mRNA expression is reduced in cirrhotic livers,[31] TPO remains the major regulator of megakaryocyte maturation and platelet production.[37] Several studies have confirmed the importance of TPO in patients with CLD. Liver fibrosis (grade 3⁄4) and liver function

correlate with low TPO serum levels.[38,39] As TPO is synthesized in the liver, impaired hepatic function may reduce TPO production.[8,40,41] TPO production in various stages of cirrhosis cannot be estimated from TPO serum levels, with conflicting reports of lower, similar and slightly elevated levels (all within the normal range) compared with control patients.[41-44] This can easily be explained by the "end-organ" regulation of TPO levels through removal by platelets and megakaryocytes. TPO levels in the normal range with thrombocytopenia cannot be regarded as 'normal' – if platelet levels are low there is usually a compensatory increase in TPO to a 'normal' level.[45,46] Thus, TPO serum levels in CLD are inappropriately low for the actual degree of thrombocytopenia.[40,43-45] The study by Koike et al.[45] showed that the gradual decline in liver function in the patients with cirrhosis and thrombocytopenia was accompanied by a gradual decline in TPO production. This resulted in a low platelet production rate by the bone marrow, ruling out a high turnover state caused by increased platelet destruction in cirrhosis. Thus, TPO serum levels reflect TPO degradation by platelets and megakaryocytes and platelet turnover and not just TPO production in the liver.[40]

Low or normal platelet turnover with normal liver synthetic function yields high TPO serum levels with thrombocytopenia, whereas high turnover states lead to TPO consumption and low serum levels.[41] In the absence of information on platelet turnover, TPO levels do not yield conclusive information on TPO production in liver diseases.[31,47,48]

3.3 | TPO levels after liver transplantation

Following successful liver transplantation (either orthotopic [OLT] or heterotopic [HLT]), TPO serum levels and peripheral platelet counts appeared to normalize.[47,49] The number of platelets increased in patients with advanced-stage cirrhosis after OLT without accelerated platelet activation or platelet consumption (resulting from consumptive coagulopathy).[40] There was a weak, but significant correlation between platelet count and spleen size before OLT. Thrombocytopenia before OLT is consistent with low platelet production and probably with splenic pooling in some patients. Patients with (but not those without) thrombocytopenia before OLT showed a gradual increase in TPO serum levels within the initial 2-3 days post-OLT.[47,50] It takes several days for the increase in TPO to result in increased platelet production. The peripheral platelet count started to increase on Day 6 post-OLT, was preceded by a significant increase in reticulated platelets, the immature young platelet fraction, and most patients had peripheral platelet counts in the normal range after 2 weeks (significantly higher than before OLT).[47] This increase in peripheral platelet count is related to increased TPO production with a functioning liver graft and not simply relief of portal hypertension, which is a consequence of OLT.[41,51]

3.4 | Suppression of platelet production in the bone marrow

Indirect information about bone marrow production of thrombocytes is available from various turnover studies, but results are inconsistent and it is difficult to compare them due to different radioligand labels and methodologies. A few studies on megakaryopoiesis and thrombocytopoiesis in patients with cirrhosis and thrombocytopenia support the idea of decreased platelet production by megakaryocytes in the bone marrow as a possible cause of thrombocytopenia in cirrhosis.[45,52-54]

Suppression of platelet production in the bone marrow can also be caused by the underlying aetiology of the liver disease (e.g. HCV or alcohol).[55] Long-term alcohol abuse alters many physiological and biochemical variables (e.g. leucocytes, platelets and erythrocytes). Direct alcohol toxicity to the bone marrow and peripheral blood elements causes depressed haematopoietic cell formation, increased destruction and altered morphology and function of haematopoietic cells.[55] The exact mechanism for alcohol-induced thrombocytopenia is unclear, but it appears to be caused mainly by a direct toxic effect of alcohol on megakaryocytes, resulting in decreased production, survival time and function of platelets and, to a lesser extent, by splenomegaly and folate deficiency.[55]

Thrombocytopenia can be caused by suppression of platelet production in the bone marrow by HCV and other viral infections.[56] It has been suggested that flaviviridae, like HCV, have a direct myelosuppressive effect in humans.[57] A study using reticulated platelets in peripheral blood as a marker of thrombopoiesis showed that patients with CLD had low platelet production.[45] IFN-α-induced decreases in HCV viral load correlated with significant increases in platelet count, even in the absence of hypersplenism or platelet autoantibodies.[58,59]

3.5 | Hypersplenic thrombocytopenia

Cirrhosis is characterized by a loss of liver cell function, reduced diameter of the hepatic vascular bed, and increased splanchnic inflow, resulting in increased pressure in the portal vein, splenomegaly and subsequent thrombocytopenia via platelet sequestration.

While the normal splenic volume has been reported to range from 50 to 200 mL, splenomegaly can increase it to >1000 mL.[60] Thrombocytopenia was first attributed to portal hypertension-induced splenomegaly and splenic pooling of platelets in patients with cirrhosis 50 years ago.[61] However, clinical evidence accumulated over the years has led to the belief that the impact of splenic pooling due to portal hypertension is not as important as originally thought and interventional and/or surgical treatments aimed at reversing portal hypertension do not reliably and persistently correct thrombocytopenia.

There is conflicting evidence on the effect of surgical shunts and the less-invasive transjugular intrahepatic portosystemic shunt (TIPS) on hypersplenism in cirrhotic liver (albeit in methodologically flawed analyses), with some groups demonstrating an improvement in platelet counts after shunt procedures[62-70] and others showing no effect.[41,71-76] The majority of the studies were retrospective, with no control group. The only prospective, controlled trial of a surgical shunt, by Mutchnick et al.[75] assessed the long-term (5.5-year follow-up) effectiveness of prophylactic shunt surgery in [38] patients with portal hypertension and oesophageal varices, but without a

prior bleeding episode and [52] unoperated control subjects. The reversal of splenomegaly was greater in the shunt group (not significant). Thrombocytopenia did not improve in either group and, in fact, the incidence increased to a similar extent in both groups. The only prospective, controlled trial of a TIPS compared the course of platelet counts in 55 patients after implantation of a TIPS with 110 matched controls without shunts.[70] TIPS implantation increased platelet counts significantly (by ~20%) compared with a decrease in the control group (~17%). However, normalization of platelet counts (≥150 000/μL) was not achieved in either group.

There is conflicting evidence on the correlation between spleen size and platelet count in patients with cirrhosis, with a number of studies failing to show any correlation between either portal pressure or spleen size and the recovery of platelet count,[47,69,77] some noting a trend,[75] and others showing a potential relationship.[78,79]

Splenectomy and splenic artery embolization have been used successfully to improve thrombocytopenia (probably by prolonging platelet survival time) in patients with hypersplenism, with several groups reporting significant increases in platelet count,[80-86] but the effect seems to be transient.[87] Used prophylactically, splenic artery embolization can improve thrombocytopenia in patients with HCV-induced cirrhosis and hypersplenism, thus facilitating antiviral therapy if IFN-based therapies were to be used.[88,89]

HLT normalizes thrombocytopenia and reduces hypersplenism.[90] Thus, portal hypertension plays a role in thrombocytopenia in CLD. However, it is not the main driver of thrombocytopenia in these patients and adequate liver synthetic function is essential to maintain or restore normal peripheral platelet count.

3.6 | Antiplatelet antibodies

In patients with CLD, autoantibodies against platelet surface antigens can enhance removal of platelets by the splenic and hepatic reticuloendothelial system leading to rapid platelet destruction and contribute, in part, to the occurrence of thrombocytopenia.[91,92] Patients with cirrhosis have inadequately low plasma TPO levels, higher platelet turnover and reduced platelet production, whereas HCV-induced cirrhosis appears to be associated with higher levels of serum antiplatelet antibodies, which could potentially lead to greater platelet destruction.[93] When using more sophisticated techniques to evaluate antiplatelet antibodies, a high rate of platelet antibodies has been found with other aetiologies of cirrhosis than HCV and there is a lack of correlation between the presence of antiplatelet antibodies and thrombocytopenia, even in HCV-induced liver disease.[94] Thus, it appears that platelet antibodies play little role in thrombocytopenia in cirrhosis, including HCV.

4 | THROMBOCYTOPENIA AND PLATELET TRANSFUSION

Platelet transfusion is the mainstay of clinical management of severe thrombocytopenia in patients who undergo invasive procedures.[95] However, the short duration of efficacy, risk of transfusion reactions and development of antiplatelet antibodies (alloimmunization) limit their use.[96-98]

The platelet count at which transfusions are indicated is controversial and there are no globally accepted guidelines for platelet transfusion in patients with CLD who undergo invasive procedures. Platelet transfusion is generally not necessary for uncomplicated patients (without CLD) with platelet counts >20 000/μL, whereas it is given routinely before interventions for platelet counts <20 000/μL.[97,99] Due to a large body of clinical trial evidence indicating that a platelet threshold of 20 000/μL is unnecessary and potentially harmful in patients not at risk for haemorrhage, there is growing support for lowering the trigger for transfusions to 10 000/μL, whereas patients with a greater risk for bleeding (e.g. surgical patients or those with infection or splenomegaly) may require higher transfusion thresholds of 50 000-100 000/μL.[100-103] In patients with CLD, the threshold for platelet transfusion before invasive procedures or major surgery varies in the published literature, depending upon the patient population and the perceived risk of the planned procedure. The typically recommended threshold of 50 000/μL is based only upon expert opinion and it is likely that many transfusions are unnecessary and subject patients to risk with little or no additional benefit.[100-103]

Because of the limitations and possible risks associated with platelet transfusion (and other management strategies, such as splenic artery embolization, TIPS and splenectomy), there has been substantial interest in novel treatments to stimulate endogenous production of functional platelets.

5 | NEW THERAPEUTIC OPTIONS FOR THROMBOCYTOPENIA IN CLD

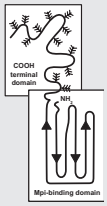
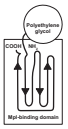
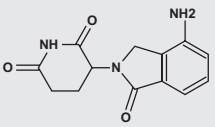
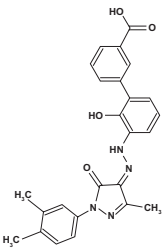
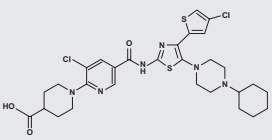
Due to the relatively recent advances in our understanding of the biology of thrombopoiesis in CLD, the key role of TPO in thrombopoiesis regulation and the changes in TPO production or activity in CLD, a variety of compounds simulating TPO activity have been developed or are in development, including IL-11, recombinant TPO, TPO mimetics and other agents (Table 1).

5.1 | Recombinant human cytokines

Subcutaneous injection of recombinant human IL-11 (rhIL-11) stimulates progenitor stem cells and production of megakaryocytes and platelets. rhIL-11 has been approved by the FDA for prevention of severe thrombocytopenia following myelosuppressive chemotherapy for solid tumours; however, it can cause significant toxicities, including oedema, fluid retention, cardiovascular events and occasionally myalgias and arthralgias.[105,106]

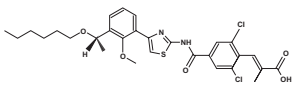
Other cytokines (e.g. IL-1, IL-3, IL-6) exert potent thrombopoietic activity, but their clinical utility has been severely limited by significant proinflammatory properties that induce flu-like symptoms, including hypotension, fatigue and myalgias.[106]

TABLE 1 TPO receptor agonists for treatment of thrombocytopenia in CLD[30,104-110]

Compound	Administration route	Chemical formula & structure	Dose	PK data	Status/indication
rhIL-11 (Recombinant human interleukin-11; oprelvekin)	Subcutaneous	$C_{854}H_{1411}N_{253}O_{235}S_2$	50 μg/kg QD	$T_{½}$: 7 h (healthy)	Approved for prevention of chemotherapy-induced severe thrombocytopenia and thrombocytopenia in adults with cirrhosis[105]
rhTPO (Recombinant human thrombopoietin)	Intravenous		—	$T_{½}$: 24-40 h	Clinical development halted
PEG-rHuMGDF (Pegylated recombinant human megakaryocyte growth and development factor)	Subcutaneous		—	$T_{½}$: 31 h	Clinical development was halted by Amgen in 1998 due to neutralizing anti-TPO antibodies[106]
Romiplostim	Subcutaneous	$C_{2634}H_{4086}N_{722}O_{790}S_{18}$ 	1-10 μg/kg QW	$T_{½}$: 3.5 d	Approved in the USA and Europe for the treatment of chronic ITP in treatment-refractory adults[107,108]
Eltrombopag (small-molecule platelet growth factor)	Oral	$C_{25}H_{22}N_4O_4$ 	25-75 mg QD (ITP) 25-100 mg QD (HCV) 50-150 mg QD (SAA)	$T_{½}$: 21-32 h (healthy) & 26-35 h (ITP)	Approved for use in patients with treatment-refractory chronic ITP or SAA, as well as for the treatment of thrombocytopenia in patients with chronic HCV infections, to allow for PEG-IFN-based therapy [108,109]
Avatrombopag (small-molecule TPO agonist)	Oral	$C_{29}H_{34}Cl_2N_6O_3S_2$ 	—		In Phase III trials for the treatment of thrombocytopenia associated with liver disease prior to an elective procedure; Filing planned for 2017

(continues)

TABLE 1 (continued)

Compound	Administration route	Chemical formula & structure	Dose	PK data	Status/indication
Lusutrombopag (small-molecule TPO agonist)	Oral	$C_{29}H_{32}Cl_2N_2O_5S$ 	3 mg QD	$T_{½}$: 38 h (CLD)	Approved in Japan for thrombocytopenia associated with CLD in patients undergoing an elective invasive procedure; In Phase III in Europe, Canada and the USA for thrombocytopenia associated with CLD

5.2 | Recombinant human TPO

Although the first-generation therapeutic TPO receptor agonists, recombinant human TPO (rhTPO) and pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF), were efficacious in clinical trials, clinical development was halted due to the formation of neutralizing autoantibodies that cross-reacted with inactivated endogenous TPO.[30,111,112]

5.3 | TPO mimetics

In the last decade, several promising TPO receptor agonists with no homology to endogenous TPO have been investigated, primarily for the management of chronic immune thrombocytopenia (ITP). Here, we report the limited number of trials in thrombocytopenia associated with HCV and CLD.

5.3.1 | Romiplostim

Romiplostim is a TPO agonist that is composed of four identical TPO-mimetic peptides attached via glycine bridges to an IgG heavy-chain Fc molecule. It avoids cross-reactive antibodies as it does not have any sequence homology to endogenous TPO and binds directly to the TPO receptor to initiate signalling pathways.

In the USA, romiplostim is indicated only for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.[107] In Europe, romiplostim is indicated for chronic ITP splenectomized adults, who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).[106]

A single-centre, single-arm, open-label study involving 35 Egyptian male patients with CLD and severe thrombocytopenia secondary to HCV infection, investigated preoperative subcutaneous romiplostim injection at 2 μg/kg once weekly (QW) over a maximum of 4 weeks or until two consecutive visits with a platelet count ≥70 000/μL.[113] Platelet counts increased to a level acceptable for elective surgical interventions in 94% of patients. This was achieved rapidly (between Days 12 and 18). Headache was the only adverse event (AE) reported, with no bleeding episodes or thromboembolic complications within 60 days of the procedure.

Participant recruitment to a double-blind, placebo-controlled Phase II trial assessing romiplostim QW in persistently thrombocytopenic patients with HCV infection before antiviral treatment with PEG-IFN and ribavarin has been suspended (ClinicalTrials.gov Identifier: NCT01153919). An interim analysis is expected.

5.3.2 | Eltrombopag

Eltrombopag is an orally available, small-molecule non-peptide TPO receptor agonist. It binds to the transmembrane domain of the TPO receptor to activate intracellular signal transduction pathways. This induces proliferation and differentiation of megakaryocyte precursors and megakaryocytes, which increases platelet count.[114,115]

Eltrombopag has received FDA and EMEA approval. It is approved for: the treatment of thrombocytopenia in adult and paediatric (USA only) patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy; in patients with chronic HCV infection to allow the initiation and maintenance of IFN-based therapy; and in patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy[108] and (Europe only) are unsuitable for haematopoietic stem cell transplantation.[109] There is a boxed warning that eltrombopag in combination with IFN and ribavirin may increase the risk of hepatic decompensation in patients with chronic HCV.

A Phase II multicentre (USA and Europe), randomized trial assessed eltrombopag 30, 50 or 75 mg once daily (QD) in 74 patients with thrombocytopenia associated with chronic HCV-related cirrhosis (platelet counts 20 000-<70 000/μL).[116] After 4 weeks, platelet count increased dose dependently to ≥100 000/μL in 75%, 79% and 95% of patients treated with 30, 50 and 75 mg eltrombopag, respectively, compared with 0% in the placebo group (P<.001). PEG-IFN and ribavirin could then be initiated, with continuation of eltrombopag or placebo for 12 additional weeks. Antiviral therapy was initiated in 49 patients (10/14 on 30 mg, 14/19 on 50 mg and 21/23 on 75 mg eltrombopag and 4/18 on placebo). Significantly more eltrombopag than placebo-treated patients completed 12 weeks of antiviral therapy (36%, 53% and 65% in the 30, 50 and 75 mg groups vs 6% in the placebo group). Three-quarters of these patients had platelet counts above baseline values at the end of the antiviral treatment phase. The most common AEs included headache, dry mouth, abdominal pain and nausea.

A Phase II trial in 38 Japanese patients with CLD and thrombocytopenia (platelets <50 000/μL) found that eltrombopag improved thrombocytopenia, with mean increases in platelet count from baseline to Week 2 of 24 800, 54 000 and 60 000/μL with 12.5, 25 and

37.5 mg respectively.[117] After eltrombopag administration (at the higher doses), platelet count increased gradually to reach a maximum after 2-4 weeks and the effect lasted for at least 1 week post-treatment (Figure 3).

The ELEVATE Phase III study (Eltrombopag Evaluated for Its Ability to Overcome Thrombocytopenia and Enable Procedures) randomized 292 patients with CLD of diverse causes and a platelet count <50 000/μL to eltrombopag 75 mg QD or placebo for 14 days before an elective invasive procedure (performed within 5 days of the last dose).[118] The primary endpoint of avoidance of platelet transfusion before, during, and up to 7 days after the procedure was achieved in 72% of the eltrombopag group vs 19% of the placebo group (*P*<.001). Bleeding episodes ≥WHO grade 2 were reported in 17% of eltrombopag patients and 23% of placebo patients (*P*=NS). The most frequently reported side effects were headache, pyrexia, abdominal pain, diarrhoea, nausea and hepatic encephalopathy. There was an increased incidence of portal-vein thrombosis with eltrombopag (n=6 vs 1 in the placebo group). Five of the six patients had their event while the platelet count was >200 000/μL (the maximum count achieved during the trial). This resulted in early study termination. An association between platelet counts >200 000/μL and increased risk of thrombotic events was subsequently identified in a *post hoc* analysis.[15]

The other two International (23 countries), multicentre, randomized, Phase III trials only included patients with chronic HCV infection and platelet levels <75 000/μL. Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitic C-Related Liver Disease (ENABLE)-1 and ENABLE-2 assessed the ability of eltrombopag to increase the platelet count and thereby enable subjects to initiate and maintain antiviral treatment with PEG-IFN and ribavarin.[119] Both trials had an initial 2-9-week open-label phase using eltrombopag to increase platelet count above a predefined threshold for antiviral initiation (ENABLE-1: ≥90 000/μL, using PEG-IFN-2α; and ENABLE-2: ≥100 000/μL, using PEG-IFN-2β). This threshold was achieved in 95% of patients in ENABLE-1 and 94% in ENABLE-2. Patients were then randomized 2:1 to eltrombopag:placebo (n=715 in ENABLE-1 and n=805 in ENABLE-2) for the whole course of antiviral treatment (24-48 weeks). Dose titration of eltrombopag was permitted.

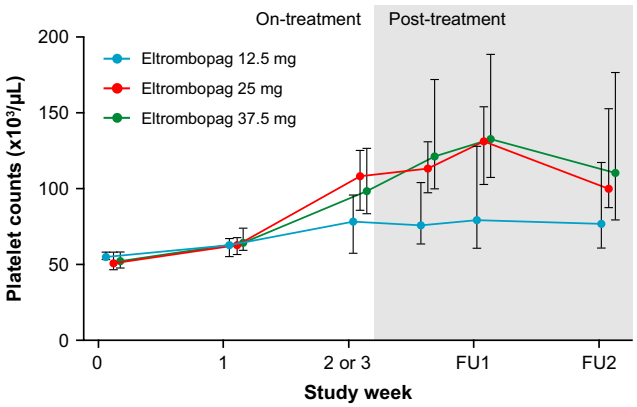


FIGURE 3 Platelet kinetics (median platelet count) after administration of eltrombopag in Japanese patients with CLD and thrombocytopenia.[117] Platelet counts after the end-of-treatment include the values after invasive procedures or platelet transfusions. Data are expressed as medians with interquartile ranges (IQRs). FU=follow-up. Republished with permission of the Journal of Gastroenterology, Springer Japan KK, from Efficacy and safety of eltrombopag in Japanese patients with chronic liver disease and thrombocytopenia: a randomized, open-label, phase II study, Kawaguchi T, Komori A, Seike M et al., 47 (12), 1342-1351. Copyright ©2008; permission conveyed through Copyright Clearance Center, Inc. [Colour figure can be viewed at wileyonlinelibrary.com]

In both trials, significantly more eltrombopag than placebo patients achieved a sustained virological response after 24 weeks of antiviral therapy (primary endpoint); the absolute benefit over placebo was <10% (eltrombopag=23% vs placebo=14% in ENABLE-1 [*P*=.0064]; eltrombopag=19% vs placebo=13% in ENABLE-2 [*P*=.0202]). Rates of early viral and end-of-treatment responses were substantially better in eltrombopag patients, as more patients could receive the full dose and less had to be stopped (Table 2). More patients on eltrombopag maintained a platelet count ≥50 000/μL (ENABLE-1=69% vs 15% with placebo; ENABLE-2=81% vs 23% with placebo) and for ~7 times longer (pooled data median time: 24.1 weeks vs 3.1 weeks with placebo). AEs were high and comparable between the eltrombopag and placebo groups (93%-97%). The most common AEs were anaemia, neutropenia, pyrexia and fatigue (Table 2). During the antiviral treatment phase, serious AEs were more common with eltrombopag in both studies (20% vs 15% with placebo). Eltrombopag was associated with an increased risk of hepatic decompensation (10% vs 5% with placebo) and thromboembolic events (3% vs 1% with placebo). A follow-up study of patients who experienced thromboembolic events in the ENABLE trials was completed in September 2016 (ClinicalTrials.gov Identifier: NCT01715779).

The status of SQUELCH-C, an open-label Phase II/III pilot study on the use of quadruple therapy with eltrombopag in combination with standard of care (PEG-IFN, ribavarin and boceprevir) in chronic HCV patients with low platelet counts (<75 000/μL) is unknown and it is likely that recruitment has been suspended (ClinicalTrials.gov Identifier: NCT01821625). Primary completion was scheduled for April 2016.

5.3.3 | Avatrombopag

Avatrombopag (E5501, YM477, AKR-501) is an oral, small-molecule TPO receptor agonist. As with eltrombopag, it binds to the TPO receptor to bring about a number of cellular reactions that give rise to megakaryocytic proliferation and differentiation and thereby platelet production.[120,121]

A Phase II study investigated avatrombopag administered 1 week before elective invasive procedures in 130 cirrhotic patients with thrombocytopenia (10 000-58 000/μL).[122] Patients were randomized to placebo vs a first-generation avatrombopag formulation (100 mg loading dose then 20, 40 or 80 mg/d on Days 2-7; cohort A; n=67) or placebo vs a second-generation formulation (80 mg loading dose then 10 mg/d on Days 2-7 or 20 mg/d on Days 2-4; cohort B; n=63).

TABLE 2 Adverse events with TPO agonists

TPO agonists	Study	Patient population	Efficacy	Safety
Romiplostim	Single-arm open-label study of 2 μg/kg QW over a maximum of 4 wk[113]	35 Egyptian men with CLD and severe thrombocytopenia secondary to HCV infection (platelet count ≤50 000/μL)	94% reached a platelet count ≥70 000/μL (primary endpoint)	Headache was the only AE reported No serious AEs No post-operative bleeding episodes No thromboembolic complications within 60 d after elective procedure
Eltrombopag	Phase II, 4- + 12-wk study of 30, 50 or 75 mg QD[116]	N=74 European and US patients with chronic HCV-induced cirrhosis (platelet count 20-70 000/μL)	75%-95% reached a platelet count ≥100 000/μL at Week 4 (primary endpoint) 66% started antiviral therapy 36%-65% completed 12 wk of antiviral therapy	During the 4-wk initial phase: Any AE: 53%-79% (vs 56% with placebo) Headache: 16%-36% (vs 17% with placebo) Dry mouth: 9%-14% (vs 6% with placebo) Upper abdominal pain: 0%-14% (vs 0 with placebo) Nausea: 4%-11% (vs 0 with placebo) Seven serious AEs during the entire study: Ascites (30 mg eltrombopag, patients withdrew) Retinal exudates (75 mg eltrombopag, patient withdrew) Thrombocytopenia (30 mg eltrombopag) Myositis (50 mg eltrombopag) Abdominal pain and renal failure (placebo, patient died)
	Phase II, 2- + 2-wk study of 12.5, 25 or 37.5 mg QD[117]	N=38 Japanese patients with CLD (platelets <50 000/μL)	Mean increases in platelet count from baseline to Week 2 of 24 800-60 000/μL (primary endpoint)	Any AE: 50%-75% Back pain: 0%-33% Pyrexia: 0%-21% Post-operative fever: 0%-25% Pleural effusion, abdominal distension, ascites, procedural pain, ALT increase, and AST increase: all 0%-17% No discontinuations Two serious AEs (both with 37.5 mg): Worsening pleural effusion and development of portal-vein thrombosis following partial splenic embolization Worsening ascites (the patient died 149 d after the end of eltrombopag treatment)
	Phase III ELEVATE study of 75 mg QD for 14 d before an elective invasive procedure[118]	N=292 with CLD (platelet count <50 000/μL)	Platelet transfusion was avoided in 72% (primary endpoint)	Any AE: 59% (vs 59% with placebo) Headache: 8% (vs 4% with placebo) Pyrexia: 6% (vs 7% with placebo) Abdominal pain: 5% (vs 5% with placebo) Diarrhoea: 5% (vs 3% with placebo) Nausea: 5% (vs 3% with placebo) Early study termination due to six portal-vein thrombotic events in the eltrombopag group
	Phase III 2-9-wk open-label + 24-48 wk randomized study ENABLE-1[119]	N=715 with HCV-induced cirrhosis (platelet count <75 000/μL)	95% reached the threshold of ≥90 000/μL and initiated PEG-IFN-2α 23% achieved a sustained virological response after 24 wk of antiviral therapy (primary endpoint)	Open-label phase: Any AE: 37% Antiviral treatment phase: Any AE: 96% (vs 97% with placebo) Anaemia: 41% (vs 34% with placebo) Neutropenia: 38% (vs 41% with placebo) Fatigue: 31% (vs 26% with placebo) Pyrexia: 31% (vs 23% with placebo) Headache: 24% (vs 20% with placebo) Nausea: 19% (vs 13% with placebo) Diarrhoea: 19% (vs 12% with placebo) Insomnia: 18% (vs 19% with placebo) Decreased appetite: 17% (vs 13% with placebo) Cough: 17% (vs 15% with placebo) Leucopenia: 16% (vs 17% with placebo) Influenza-like illness: 16% (vs 17% with placebo) Pruritus: 15% (vs 12% with placebo) Asthenia: 15% (vs 15% with placebo) Thrombocytopenia: 15% (vs 37% with placebo) Serious AE: 20% (vs 15% with placebo) 10% developed hepatic decompensation (vs 5% with placebo) & 3% developed thromboembolic events (vs 1% with placebo)

(continues)

TABLE 2 (continued)

TPO agonists	Study	Patient population	Efficacy	Safety
	Phase III 2-9-wk open-label + 24-48 wk randomized study ENABLE-2[119]	N=805 with HCV-induced cirrhosis (platelet count <75 000/μL)	94% reached the threshold of ≥100 000/μL and initiated EG-IFN-2β 19% achieved a sustained virological response after 24 wk of antiviral therapy (primary endpoint)	Open-label phase: Any AE: 34% Antiviral treatment phase: Any AE: 94% (vs 93% with placebo) Anaemia: 40% (vs 36% with placebo) Pyrexia: 28% (vs 24% with placebo) Neutropenia: 27% (vs 33% with placebo) Fatigue: 25% (vs 21% with placebo) Influenza-like illness: 20% (vs 14% with placebo) Headache: 19% (vs 20% with placebo) Diarrhoea: 19% (vs 10% with placebo) Decreased appetite: 19% (vs 15% with placebo) Nausea: 18% (vs 15% with placebo) Asthenia: 17% (vs 12% with placebo) Insomnia:14% (vs 11% with placebo) Pruritus: 14% (vs 13% with placebo) Cough: 13% (vs 10% with placebo) Leucopenia: 11% (vs 13% with placebo) Thrombocytopenia: 12% (vs 33% with placebo) Serious AE: 20% (vs 15% with placebo) 10% developed hepatic decompensation (vs 5% with placebo) & 3% developed thromboembolic events (vs 1% with placebo)
Avatrombopag	Phase II study of two cohorts of avatrombopag (first-generation formulation 100 mg loading dose then 20, 40 or 80 mg QD on Days 2-7 cohort A; second-generation formulation 80 mg loading dose then 10 mg QD on Days 2-7 or 20 mg QD on Days 2-4 cohort B) given 1 wk before elective invasive procedures[122]	N=130 with CLD (platelet count 10-58,000/μL)	49% in Cohort A and 48% in cohort B achieved a platelet count increase ≥20 000/μL from baseline and >50 000/μL at least once during Days 4-8 (primary endpoint)	Any AE: Cohort A 84% (vs 75% with placebo); Cohort B 83% (vs 76% with placebo) Nausea: Cohort A 10% (vs 13% with placebo); Cohort B 17% (vs 14% with placebo) Fatigue: Cohort A 10% (vs 6% with placebo); Cohort B 10% (vs 19% with placebo) Headache: Cohort A 10% (vs 13% with placebo); Cohort B 10% (vs 14% with placebo) Portal hypertensive gastropathy: Cohort A 12% (vs 0 with placebo); Cohort B 7% (vs 10% with placebo) Abdominal pain: Cohort A 12% (vs 0 with placebo); Cohort B 5% (vs 14% with placebo) Vomiting: Cohort A 12% (vs 0 with placebo); Cohort B 2% (vs 5% with placebo) Diarrhoea: Cohort A 8% (vs 0 with placebo); Cohort B 7% (vs 10% with placebo) Dizziness: Cohort A 6% (vs 6% with placebo); Cohort B 10% (vs 5% with placebo) Pyrexia: Cohort A 4% (vs 13% with placebo); Cohort B 2% (vs 14% with placebo) Serious AE: Cohort A 16% (vs 6% with placebo); Cohort B 19% (vs 14% with placebo) One patient (100/80 mg avatrombopag cohort A group) had a portal-vein thrombosis during post-treatment follow-up
Lusutrombopag	Phase IIB, 7d study of 2, 3 or 4 mg QD[123]	N=61 with CLD (platelet count 41 000/μL at baseline)	80%-93% did not require a platelet transfusion prior to percutaneous liver ablation (primary endpoint) Mean maximum platelet count increased to 74-104 000/μL	Any AE: 94% (vs 100% with placebo) Thrombotic events: 0%-13% (vs 6% with placebo)

(continues)

TABLE 2 (continued)

TPO agonists	Study	Patient population	Efficacy	Safety
	Phase III L-PLUS 1 study of 3 mg QD for up to 7 d before an elective invasive procedure [124,125]	N=96 Japanese patients with CLD (platelet count <50 000/μL)	79% did not require a platelet transfusion prior to the scheduled procedure (primary endpoint) Median maximum platelet count increased to 87 000/μL	Any AE: 98% (vs 100% with placebo) Pyrexia: 40% (vs 56% with placebo) Procedural pain: 46% (vs 42% with placebo) Procedural hypertension: 42% (vs 38% with placebo) Increased AST 23% (vs 31% with placebo) Bleeding-related AEs: 15% (vs 27% with placebo) No clinically significant changes were observed in portal blood flow Protocol-required CT/MRI revealed one thromboembolic event of the portal venous system in each treatment arm (both unrelated to platelet count)

There was a high number of Child–Pugh A patients with platelet count 10 000-50 000/μL at baseline (~40%). Invasive procedures performed were mostly endoscopies (very low bleeding risk). The primary endpoint (platelet count increase ≥20 000/μL from baseline to >50 000/μL at least once during Days 4-8) was achieved by 49.0% of avatrombopag-treated vs 6.3% of control patients in cohort A (P<.001) and 47.6% vs 9.5% in cohort B (P=.009). The increase in platelet count reached a maximum 76.5% response in the 100/80 mg group in Cohort A. Possibly or probably treatment-emergent/serious AEs occurred in 29.0%/10.8% of placebo- vs 29.7%/17.9% of avatrombopag-treated patients (both cohorts combined; Table 2).

Two additional Phase II studies of avatrombopag have been completed recently (ClinicalTrials.gov Identifiers: NCT02227693 in Japanese subjects with CLD and thrombocytopenia and NCT01355289 in subjects with chronic HCV-related thrombocytopenia who are potential candidates for antiviral treatment).

Two Phase III trials of avatrombopag for adults with thrombocytopenia associated with liver disease prior to an elective procedure are currently recruiting patients (ClinicalTrials.gov Identifiers: NCT01976104 and NCT01972529). Data are expected in December 2016.

5.3.4 | Lusutrombopag

Lusutrombopag is a chemically synthesized, oral, small-molecule human TPO agonist that activates the signal transduction pathway in the same fashion as endogenous TPO to upregulate platelet production.

Lusutrombopag has been approved in Japan for thrombocytopenia associated with CLD in patients undergoing an elective invasive procedure. One Phase III study in thrombocytopenia associated with CLD in Japan has been completed and one Phase III trial in European and North American countries is underway.

Two Phase II studies of lusutrombopag as pretreatment for percutaneous radiofrequency ablation (RFA) in Japanese patients with CLD and thrombocytopenia have been completed, but data are not in the public domain (Clinical trial identifiers: JapicCTI-111625, JapicCTI-101377). In a Phase IIB, multicentre, randomized, double-blind study of lusutrombopag (2, 3 and 4 mg QD) vs placebo administered for up to 7 days in 61 CLD patients (Child–Pugh A or B) with severe thrombocytopenia (baseline mean platelet count 41 000/μL), the proportion of patients who did not require platelet transfusion prior to RFA (primary endpoint) was significantly greater (P<.005) with lusutrombopag, ranging from 80% with 2 mg to 93% with 4 mg vs 20.0% with placebo.[123] There was a dose-dependent increase in mean maximum platelet count with lusutrombopag ranging from 74 000/μL with 2 mg to 104 000/μL with 4 mg vs 59 000/μL with placebo. Lusutrombopag was generally well tolerated, and no dose-limiting AEs occurred (Table 2). The incidence of (transient) thrombotic events was low (2 mg=1, 3 mg=0, 4 mg=2, placebo=1).

In a Japanese, Phase III, double-blind study in patients with thrombocytopenia associated with CLD scheduled to undergo elective invasive procedures (L-PLUS 1), patients were randomized to lusutrombopag 3 mg QD (n=48) or placebo (n=48) for up to 7 days and stratified by the type of scheduled invasive procedure and platelet count at screening.[124,125] Significantly greater proportions of lusutrombopag than placebo patients did not require platelet transfusion prior to the scheduled invasive procedure (primary endpoint; 79.2% vs 12.5%, respectively; P<.0001) and responded (platelet count ≥50 000 and ≥20 000/μL greater than baseline; 77.1% vs 6.3%, respectively; P<.0001). Details of the most common AEs, the incidence of bleeding-related AEs and thromboembolic events are given in Table 2.

Data from a global, Phase III study of lusutrombopag 3 mg vs placebo for thrombocytopenia in patients with CLD scheduled to undergo elective invasive procedures (L-PLUS 2) are expected in November 2016 (ClinicalTrials.gov Identifier: NCT02389621). Recruiting has begun in Japan for a Phase IIIB trial to assess the pharmacokinetics, efficacy and safety of lusutrombopag in CLD patients with thrombocytopenia prior to invasive procedures (JapicCTI-153023) and a separate study in Child–Pugh C patients (JapicCTI-163289).

6 | CONCLUSIONS

Haematologic and coagulation abnormalities are frequent in people with CLD. Thrombocytopenia (defined as <50 000/μL) is a major risk factor and independent predictor for bleeding with medical interventions, such as surgical procedures and antiviral therapy. The aetiology of thrombocytopenia in liver disease is multifactorial and likely due to

a combination of portal hypertension and splenic sequestration with decreased production of TPO, the predominant endogenous thrombopoietic growth factor, by the diseased liver. Administration of rH-TPO or its synthetic C-terminally truncated and pegylated analogue, rHuMGDF showed promise, but production of neutralizing antibodies that cross-reacted with the endogenous molecule in Phase I studies led to the halting of their clinical development. A number of TPO agonists are currently available or in development to manage thrombocytopenia in patients with CLD undergoing invasive diagnostic procedures or surgery, as well as patients with ITP, myelodysplastic syndrome, chemotherapy-induced severe thrombocytopenia and HCV-related thrombocytopenia. It has been shown clearly that these TPO agonists increase the platelet count reliably in patients with thrombocytopenia due to cirrhosis, indicating that TPO deficiency seems to be pathophysiologically relevant and can be overcome by substitution. Nevertheless, despite proof-of-concept evidence that TPO agonists ameliorate IFN-induced thrombocytopenia during antiviral therapy for HCV and improve treatment success, results are unconvincing due to disputable ways of reaching the endpoints in these trials and the relevant number of decompensations in treatment groups. However, this has little relevance today in an era of oral HCV treatments. The main indications for TPO agonists in patients with CLD will be the peri-interventional management of thrombocytopenia and, unless the ongoing trials show a relevant number of adverse thrombotic events, they can be expected to gain rapid and wide-spread acceptance for this indication soon.

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CONFLICT OF INTEREST

I have the following conflict of interest to declare: Investigator for Shionogi and a speaker/advisor for Amgen, Glaxo and Shionogi.

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