Guide to the management of severe thrombocytopenia in patients with chronic liver disease

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This guide was organised and funded by Shionogi

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Gastrointestinal Nursing

December 2021, PP-UK-LUS-0358

Prescribing information and adverse events reporting can be found on page 8.

Thrombocytopenia (TCP) is a common haematological complication observed in patients with cirrhosis (*Box 1*). It is defined as a platelet count <150 000 cells/µl of blood (<150 x 10^9 cells/l) (Afdhal et al, 2008). Platelet counts correlate with severity (*Table 1)*. When platelet levels fall below 50 x 10^9 cells/l, there is an increased risk of bleeding during an invasive procedure such as liver biopsy or surgery. This increases morbidity and the risk of life-threatening complications, and can delay planned treatments (Giannini, 2006; Poordad, 2007).

Reduced platelet counts in people with chronic liver disease (CLD) can be due to decreased platelet production, platelet sequestration and increased platelet destruction.

A major driver in the development of TCP is the reduced production of thrombopoietin (TPO) that can occur in the presence of CLD. Produced in the liver, TPO is a growth factor that stimulates production of platelets from megakaryocytes in the bone marrow. Reduced levels of TPO are thus associated with decreased platelet production.

This guide focuses on the relationship between TPO and platelet production.

Box 1. Reported incidence of thrombocytopenia

- Observed in 64% of people (64/100) with bridging fibrosis or cirrhosis and 5.5% of patients (5/91) with chronic hepatitis

Source: Bashour et al (2000)

Table 1. Categories of thrombocytopenia severity

Category	Platelet count: cells/l
Thrombocytopenia	<150 x 10^9/l
Mild TPO	100–150 x 10^9/l
Moderate TPO	50–99 x 10^9/l
Severe TPO	<50 x 10^9/l

TPO=thrombopoietin
Sources: Gangireddy et al (2014); Peck-Radosavljevic (2017)

Regulation of thrombopoietin production

Figure 1 illustrates the relationship between TPO and platelet production. It shows the critical role of TPO in maintaining platelet levels. If liver dysfunction is present, TPO production decreases and, with it, the stimulus for platelet production. When normal liver function is restored, platelet production returns to normal.

Management of patients undergoing invasive procedures

At present, in patients with TCP, a platelet transfusion is used to increase platelet levels before an invasive procedure.

The consensus of three key guidelines is that patients undergoing invasive procedures such as a liver biopsy should have a platelet count of >50 000/µl (National Institute for Health and Care Excellence (NICE), 2015; Estcourt et al, 2017; O'Leary et al, 2019).

Table 2 lists procedures associated with a risk of bleeding. Those associated with a higher risk of bleeding or adverse consequences of it, such as neurosurgery or ophthalmic surgery, may require a platelet count of 100 000/µl (Estcourt et al, 2017).

Challenges of platelet transfusion

The lifespan of platelets is normally about 10 days; the half-life of transfused platelets can be as low as 2.5–4.5 days (O'Leary et

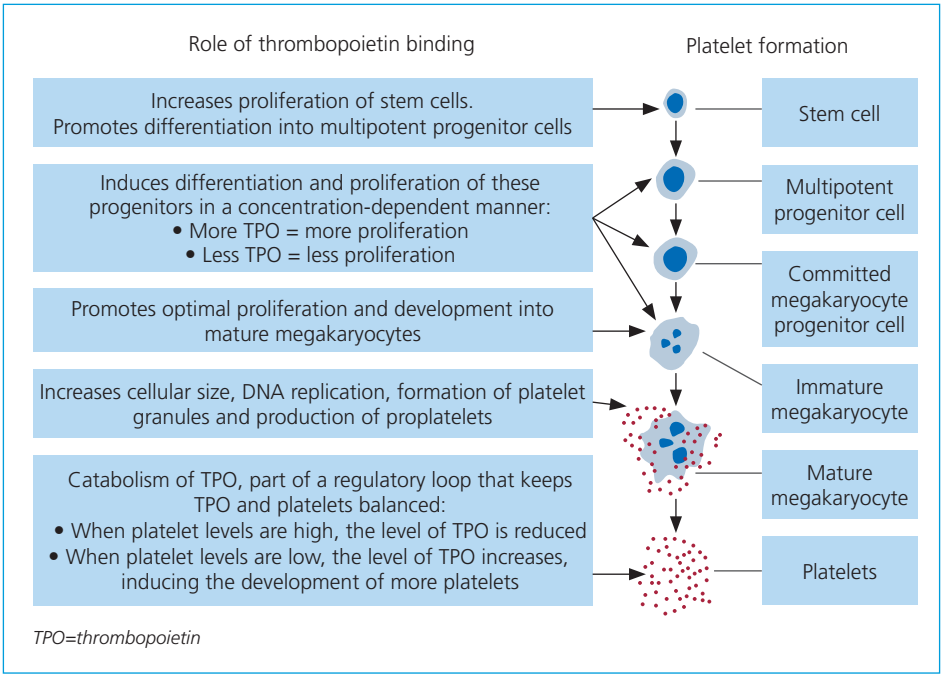

Figure 1. Role of thrombopoietin on platelet production (adapted from Peck-Radosavljevic et al, 2017)

al, 2019). A 250 ml platelet transfusion can typically increase the platelet count by 5000/µl, to 10 000/µl (O'Leary et al, 2019). More than one dose may thus be needed to increase the platelet count to an acceptable pre-procedure level. However, supply is a problem. In 2008–2015, clinical demand for platelets rose by 25%, but the number of blood donors has continued to fall (Estcourt et al, 2017).

The practical and clinical challenges associated with platelet transfusion are summarised in *Box 2*. The decision to transfuse is based on the patient's platelet count, international normalised ratio (INR) blood test results, concurrent prescribed medications, history of bleeding and the risks associated with the planned procedure.

Given the multiple challenges associated with platelet transfusion, the TPO receptor agonist drugs are a sensible alternative when a procedure is planned.

Alternative treatment options

Recognition of the role of TPO in maintaining platelet levels led to exploration of potential new therapeutic agents that can stimulate its production or activity in people with CLD.

Early unlicensed agents

These included:

- Interleukin-11, a cytokine originally thought to be important for megakaryocyte maturation; however, this was subsequently found to be associated with toxic side effects such as cardiovascular events and oedema (Peck-Radosavljevic, 2017)

Table 2. Examples of procedures with risk of bleeding*(adapted from Intagliata et al, 2018)

High-risk procedures	Intermediate-risk procedures	Low-risk procedures
Brain or spinal surgery	Lumbar puncture	Paracentesis
All major surgery (cardiac, intra-abdominal and orthopaedic)	Percutaneous or transjugular liver biopsy	Thoracentesis
Intracranial pressure catheter insertion	Transjugular intrahepatic portosystemic shunt (TIPS). Dental extraction	
Therapeutic endoscopy (large polypectomy with endoscopic mucosal or submucosal resection, natural orifice transluminal endoscopy (NOTES))	Therapeutic endoscopy (eg, percutaneous gastrostomy placement, cystogastrostomy, biliary sphincterotomy)	Diagnostic endoscopy
	Percutaneous biopsy of extrahepatic organ or lesions	Cardiac catheterisation
	Transarterial or percutaneous hepatocellular carcinoma (HCC) therapies (TACE, RFA)	Central-line placement

TACE = transarterial chemoembolisation; RFA = radiofrequency ablation.
**Risk is based on vascularity, extent of likely vascular breach and clinical consequences of bleeding. An individual patient's risk status should be defined by the clinician preforming the procedure.*

- Pegylated human recombinant megakaryocyte growth and development factor, and a recombinant TPO, both of which were halted in development because of the emergence of neutralising TPO antibodies (Peck-Radosavljevic, 2017)
- Eltrombopag, a TPO mimetic agent. However, a study by Afdhal et al (2012) found that 4% (6/145) people with CLD developed a portal vein thrombosis following its administration.

Second-generation treatments

The next generation of treatments for TCP are Mulpleo▼ (lusutrombopag) and avatrombopag, both oral, human TPO receptor agonists that activate the signal transduction pathway in the same way as endogenous TPO, increasing platelet production (European Medicines Agency, 2019a;b). Lusutrombopag is summarised in *Table 3*.

Two phase 3 studies have been conducted on lusutrombopag in patients with CLD: L-PLUS 1 (Hidaka et al, 2019) and L-PLUS 2 (Peck-Radosavljevic et al, 2019). The key features of these studies are summarised in *Table 4*.

Two phase 3 studies have also been conducted on avatrombopag: ADAPT-1 and ADAPT-2. These showed that between 65.6% and 87.9% of patients did not need a platelet transfusion for up to 7 days following a planned procedure (Terrault et al, 2018).

Both drugs have been approved in the US for use in patients with CLD (for a short

period) to increase the platelet count before invasive procedures (O'Leary et al, 2019). In the UK, lusutrombopag and avatrombopag have been approved for use in the EU. Lusutrombopag has also been recommended by Scottish Medicine Consortium (SMC) and recommended by NICE as an option for treating severe TCP (NICE, 2020).

Benefits for patients and the NHS

Lusutrombopag has been licensed in Japan since 2015. Post-licensing data show that 99 adverse events were reported in 4000 patients from April 2018 to October 2019 (Peck-Radosavljevic et al, 2019), supporting observations in the L-PLUS 1 and L-PLUS 2 studies that it is well tolerated (Hidaka et al, 2019; Peck-Radosavljevic et al, 2019).

Clinical data and real-world evidence show that lusutrombopag and avatrombopag are not associated with an increased risk of portal vein thrombosis (European Medicines Agency, 2019b). Lusutrombopag is prescribed as a single, oral, fixed-dosed tablet; to date, no dose adjustment is necessary.

Additional advantages for lusutrombopag over platelet transfusions are that it does not increase portal pressure (thereby reducing the risk of variceal bleeding) and that serum platelet counts can remain elevated for a longer duration (O'Leary et al, 2019).

TPO agonists also provide a treatment option previously unavailable to patients who decline blood product transfusions for a number of reasons, for example, religion.

Reducing the need for a hospital bed or day-case space to facilitate a platelet transfusion benefits both patients and the NHS. Access to an alternative to platelet transfusion, whose supply has decreased in recent years, is another advantage for the NHS. Furthermore, as the platelet response to a TPO agonist is more predictable than that to a platelet transfusion, these agonists can be used as an alternative prophylactic treatment for severe TCP/CLD patients with a high risk of bleeding. In short, lusutrombopag is an effective alternative to platelet transfusion for planned invasive procedures in patients with severe TCP and CLD who are at increased risk of bleeding.

Box 2. Challenges associated with platelet transfusion

Clinical challenges

- Unpredictable; short-term effect
- Allergic reactions
- Risk of volume overload in critically unwell patients
- Febrile non-haemolytic reactions
- Bacterial and viral contamination
- Transfusion-related lung injury
- Platelet refractoriness*
- Development of human leucocyte antigen (HLA) antibodies

Practical challenges

- High demand/limited supply of platelets
- Supply delays could potentially delay a planned procedure
- Hospital attendance is necessary for transfusion, so a bed is required

**Platelet refractoriness is defined as non-response to platelet transfusion, whereby the platelet count does not rise as a consequence of frequent platelet transfusions.*

Hayashi et al (2014); Estcourt et al (2017); Peck-Radosavljevic (2017); O'Leary et al (2019)

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Table 3. Lusutrombopag

Mechanism of action
Acts on: human thrombopoietin receptors on haematopoietic stem cells, megakaryocyte progenitor cells, immature megakaryocytes, mature megakaryocytes and platelets
Activates: pathways that promote proliferation and differentiation of bone marrow progenitor cells into megakaryocytes, thereby increasing platelet levels
Pharmacokinetics
Half-life: 38.3 hours
Effect of food on absorption: no impact (including high-fat diet) on pharmacokinetics
Renal function: renal impairment does not affect pharmacokinetics
Hepatic function: Child-Pugh class A or class B has little effect on pharmacokinetics; Child-Pugh class C patients were excluded from phase 3 trials and so the safety and efficacy of lusutrombopag in these patients has not been established

Source: Peck-Radosavljevic et al (2019), Tateishi et al (2019)

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Table 4. Summary of the L-PLUS 1 and L-PLUS 2 trials

	L-PLUS 1	L-PLUS 2
Population	Japan; 81 clinical centres	Global; 22 countries; 138 sites
Sample size	96 patients with chronic liver disease and thrombocytopenia (Child-Pugh class A and B cirrhosis)	215 patients with cirrhosis and platelet counts <50 000/µl
Study dates	October 2013 to May 2014	June 2015 to April 2017
Study medication	Randomised 1:1 to 3 mg lusutrombopag or placebo once daily over 7 days	Randomised 1:1 to 3 mg lusutrombopag or placebo once daily over 7 days
Primary outcome measure	Proportion of patients not requiring a platelet transfusion before an invasive procedure	Avoidance of pre-procedure platelet transfusion and rescue therapy
Secondary outcome measure	Platelet count above 50 000/µl, with an increase of ≥20 000/µl above baseline	Number of days platelets remained elevated above 50 000/µl
Results	Proportion of patients not requiring platelet transfusion: 79.2% (38/48) vs. 12.5% (6/48) in the lusutrombopag and placebo groups, respectively (p<0.0001) For this subgroup in the lusutrombopag group: median platelet count was ≥50 000 after 5 days; mean time to reach maximum platelet count was 13.4 days; the adjusted mean number of days during which the platelet count was ≥50 000 was 21.09	Proportion of patients not requiring platelet transfusion: 64.8% (70/108) vs. 29% (31/107) in the lusutrombopag and placebo groups, respectively (p<0.0001) The median number of days in which platelets remained above 50 000/µl were 19.2 and 0 in the lusutrombopag and placebo groups, respectively (p=0.0001).
Adverse drug events	These were reported in 8.3% (4/48) of the lusutrombopag group (nausea, headache, pyrexia, pain and portal vein thrombosis) and 2.1% (1/48) of the placebo group (hypothermia)	Overall, 47.7% (51/107) and 48.6% (52/107) of patients in the lusutrombopag and placebo groups, respectively, experienced mild or moderate adverse effects including headache, fatigue, nausea, abdominal pain and peripheral oedema
Serious adverse events	One person in each group had a portal vein thrombosis; the maximum platelets recorded were 79 000/µl vs. 60 000/µl in the lusutrombopag and placebo groups, respectively	There were three treatment-related deaths in the lusutrombopag group (which were not considered due to lusutrombopag) and none in placebo group. Two people developed a portal vein thrombosis in both the lusutrombopag and placebo groups

Sources: Hidaka et al (2019); Peck-Radosavljevic et al (2019)

Mulpleo®▼ (lusutrombopag) Prescribing Information

Mulpleo® (lusutrombopag) 3 mg film-coated tablets. Refer to full Summary of Product Characteristics (SmPC) before prescribing.

Presentation
Each film-coated tablet contains 3 mg of lusutrombopag.

Indication
Treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures.

Dosage and administration
The recommended dose is one oral tablet once daily, with or without food, for 7 days. The procedure should be performed from day 9 after the start of treatment. Platelet count should be measured prior to the procedure.

Contraindications
Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions
Caution should be exercised with respect to thromboembolic events after invasive procedures as well as post-treatment regardless of platelet counts. Patients with thrombosis or thromboembolism, with a history of thrombosis or thromboembolism, with absence of hepatopetal blood flow in the main trunk of the portal vein, or patients with congenital coagulopathy should be clinically monitored when treated with lusutrombopag. Lusutrombopag should only be used in patients with severe (Child-Pugh class C) hepatic impairment if the expected benefit outweighs the expected risks. Due to the unstable nature of these patients, they should be supported in line with clinical practice by close monitoring for early signs of worsening or new onset hepatic encephalopathy, ascites, and thrombotic or bleeding tendency, through monitoring of liver function tests, tests used for assessing clotting status and through imaging of portal vasculature as needed. In patients with Child-Pugh class C liver disease and in patients with body weight <45 kg, platelet count should be measured at least once approximately 5 days after the first dose and as necessary thereafter and appropriate measures such as discontinuation of lusutrombopag should be taken, if the platelet count reaches ≥50 000/µl as a result of a 20 000/µl increase from baseline. The efficacy and safety of lusutrombopag have not been established when administered before laparotomy, thoracotomy, open-heart surgery, craniotomy or excision of organs. Platelet count should be carefully monitored in patients with a history of splenectomy treated with lusutrombopag. Interferon preparations have been known to reduce platelet counts, therefore, this should be considered when co-administering lusutrombopag with interferon preparations. A potential interaction with either P-gp or BCRP inhibitors cannot be excluded, but no dose adjustment is necessary at the recommended clinical dosage of 3 mg in adults.

Pregnancy and lactation
Should be used with contraception, not recommended during pregnancy and in women of childbearing potential not using contraception. Should not be administered to breast-feeding women.

Undesirable effects
Common: headache, nausea, portal vein thrombosis and rash.

Legal classification
Prescription-only medicine.

MA number:
EU/1 /18/1348.

Pack sizes and cost
7 tablets £800.00.

MA holder
Shionogi B.V., Kingsfordweg 151, 1043GR, Amsterdam, The Netherlands.

Date of preparation: December 2021

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk. Adverse events should also be reported to Shionogi on 020 3053 4190 or via contact@shionogi.eu

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