Treatment algorithm for thrombocytopenia in patients with chronic liver disease undergoing planned invasive procedures

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Abstract
Thrombocytopenia is highly prevalent in patients with chronic liver disease (CLD) and these patients often require invasive procedures that carry a risk of bleeding. To prevent bleeding, guidelines recommend increasing platelet counts in patients with CLD who have thrombocytopenia and are planned to undergo invasive procedures. There are currently two options to increase platelet counts in patients in this setting: platelet transfusion or thrombopoietin receptor agonists (TPORAs). Several treatment algorithms have been developed in the US to help physicians choose the best course of treatment for each patient; however, to date, no such algorithm has been proposed in other countries, where the choice of treatment has been based on each physician’s judgment and experience. Here, we discuss the pathogenesis and treatment of thrombocytopenia in patients with CLD, we review and present current evidence of the efficacy of TPORAs for the treatment of thrombocytopenia in patients with CLD, and we present our expert opinion on a Japanese treatment algorithm for thrombocytopenia in patients with CLD who are planned to undergo invasive procedures. This algorithm aims to provide guidance for optimal decision making in the selection of TPORA therapy or platelet transfusion based on the latest evidence and according to actual clinical practice.

KEYWORDS
algorithm, blood transfusion, chronic liver disease, Japan, thrombocytopenia, thrombopoietin receptor agonist
BACKGROUND

Liver disease is a major contributing factor to the development of thrombocytopenia. The prevalence of thrombocytopenia in patients with chronic liver disease (CLD) varies depending on disease severity and the criteria used to define thrombocytopenia. In a cohort study of patients with compensated cirrhosis, 77.9% of patients had thrombocytopenia at baseline, and by the end of the study, 92.5% of the original cohort had developed thrombocytopenia. Among patients with cirrhosis, the percentages of patients with mild (defined as a platelet count of 100–150 × 10⁹/L), moderate (50–100 × 10⁹/L), and severe (<50 × 10⁹/L) thrombocytopenia have been reported to be 64%, 13%, and 1%, respectively. Low platelet count in patients with CLD is generally considered a predictor of bleeding risk during invasive procedures, and patients with CLD often require invasive procedures that carry a risk of bleeding. Therefore, in patients with CLD and thrombocytopenia who are planned to undergo invasive procedures, various guidelines recommend increasing platelet counts to avoid bleeding risk.

In general, platelet transfusions are provided for patients with thrombocytopenia who are planned to undergo an invasive procedure. However, there are some safety concerns and logistical challenges with platelet transfusions, and platelet transfusions may become less effective over time in patients with CLD. Recently, thrombopoietin receptor agonists (TPORAs) have been used for the treatment of thrombocytopenia in patients with CLD.

Regarding the choice of treatment for thrombocytopenia in patients with CLD planning to undergo invasive procedures, several treatment algorithms have been proposed in recent years by physicians in the US. These algorithms are useful tools for treatment decision making. However, in most countries, the choice of treatment is based on each physician’s judgment and may differ among medical facilities, and no consensus has been reached. Furthermore, there are discrepancies in the details included in package inserts for lusutrombopag based on region. While the use of lusutrombopag is contraindicated in patients with severe liver dysfunction (Child-Pugh class C), and not recommended in patients who are planned to undergo major surgery (e.g., laparotomy, thoracotomy, open-heart surgery, craniotomy, or evisceration) according to the Japanese package insert, no such restrictions are noted in other regional package inserts. In addition, the recent COVID-19 pandemic has triggered a decrease in the number of blood donors. In April 2020, the Japan Society of Transfusion Medicine and Cell Therapy announced an urgent proposal to address the shortage of blood products and plasma derivatives due to the spread of COVID-19. Considering the current situation, there is an unmet need for treatment guidelines specific for patients with CLD who present with thrombocytopenia, to help clinicians determine the best treatment course for each patient before undergoing an invasive procedure.

In this article, we present our expert opinion on a Japanese treatment algorithm for thrombocytopenia in patients with CLD who are planned to undergo invasive procedures. Seven experts in internal medicine, surgery, and radiology with experience treating patients with CLD in Japan participated in this discussion. A literature search was conducted on March 28, 2021 by combining multiple search terms such as (thrombocytopenia AND [cirrhosis OR CLD]), resulting in the identification of 1988 relevant articles from the year 2000 onward to be assessed by the experts. Key articles relating to the treatment of thrombocytopenia were extracted and incorporated into this review based on the experts’ evaluation. The treatment algorithm was constructed based on two discussions by the experts on February 20, 2021 and March 15, 2021.

Particularly in situations where there is a shortage of platelets for transfusion, such as during the current pandemic, it is important to choose the best treatment approach on a patient-to-patient basis, considering the bleeding risk of the invasive procedure and the patient’s condition. This algorithm has been developed to provide guidance for optimal decision making in the selection of TPORA therapy or platelet transfusion based on the latest evidence and according to actual clinical practice.

PATHOGENESIS AND TREATMENT OF THROMBOCYTOPENIA IN PATIENTS WITH CLD

Pathogenesis of thrombocytopenia and hemostatic abnormalities in patients with CLD

As mentioned previously, thrombocytopenia is highly prevalent in patients with CLD. Thrombocytopenia in patients with cirrhosis mainly occurs through the following mechanisms: (1) splenic platelet sequestration, (2) decreased production of thrombopoietin (TPO) in the liver, and (3) accelerated platelet destruction. In patients with congestive splenomegaly caused by portal hypertension due to cirrhosis, platelets are sequestrated in the spleen, thus reducing circulating platelets.

Thrombopoietin, which regulates differentiation of megakaryocytes from hematopoietic stem cell precursor cells, and platelet production from megakaryocytes, is mainly produced in the liver. In patients with cirrhosis, one of the main mechanisms of thrombocytopenia is decreased TPO production due to impaired liver function and a reduced platelet production rate.

An increased prevalence of immune thrombocytopenia has also been observed in patients with CLD. Rapid destruction of platelets may be caused by autoantibodies to platelet surface antigens.

In addition, patients with cirrhosis are relatively deficient in both coagulation and anticoagulation factors, resulting in an unstable balance between prothrombotic and prohemorrhagic states. Therefore, depending on individual risk factors, both thrombosis and bleeding disorders are possible in these patients. Indeed, patients with cirrhosis are known to be in a hypercoagulable state. Patients with cirrhosis demonstrate decreased coagulation factors and possible dysfibrinogenemia, which may be counterbalanced by a reduction in anticoagulation factors (such as activated protein C, protein S, and antithrombin) and an increase in platelet counts and other factors. For this reason, prothrombin time (PT) and
international normalized ratio (INR) may not be reliable markers for assessing bleeding risk in these patients and should be used only for prognostic prediction.24

Treatment of thrombocytopenia in patients with CLD

Platelet transfusion has traditionally been the standard of care in the treatment of thrombocytopenia in patients with CLD. However, especially in recent years, accumulated evidence from clinical trials on the efficacy of TPORAs has shown these drugs to be a useful alternative to platelet transfusion.25

In a recent systematic review, the use of TPORAs in patients with CLD undergoing planned procedures was reported to significantly increase platelet counts and decrease the incidence of platelet transfusions versus placebo.26 In addition, TPORA therapy also decreased the incidence of total peri-procedural bleeding without increasing the rate of thrombosis.

In the US algorithm for thrombocytopenia in patients with CLD, TPORAs are recommended as first-line treatment for patients with CLD and severe thrombocytopenia (platelet count <50 × 10^9/L) who are planned to undergo invasive procedures.15,17 In current guidelines for the treatment of cirrhosis in Japan, the use of TPORAs was added to the recommendations for the treatment of thrombocytopenia in patients with cirrhosis.7 The TPORAs avatrombopag and lusutrombopag are approved worldwide, and the US Food and Drug Administration recommends the use of avatrombopag or lusutrombopag for thrombocytopenic patients with CLD.5 In the UK, the National Institute for Health and Care Excellence also recommends the use of avatrombopag27 and lusutrombopag28 for the treatment of thrombocytopenia in patients with CLD who are planned to undergo invasive procedures. In Japan, lusutrombopag was approved in 2015 for the improvement of thrombocytopenia in patients with CLD undergoing planned invasive procedures.29 The dosage and administration of lusutrombopag according to the Japanese Pharmaceutical and Medical Devices agency is 3 mg orally, once daily for 7 days at 8–13 days prior to the procedure.18 Lusutrombopag was also approved for thrombocytopenia in Europe in 2018 and for severe thrombocytopenia in Japan.13

Clinical issues with platelet transfusion in patients with CLD

Globally, platelet transfusion has been the standard of care for thrombocytopenic patients planned to undergo invasive procedures, and those with platelet counts <50 × 10^9/L have been considered eligible for treatment.31,32 The 2019 Japan Society of Transfusion Medicine and Cell Therapy guidelines also recommend a platelet count of 50 × 10^9/L as the cut-off value for platelet transfusion prior to invasive procedures, and states that platelet transfusion should be maintained until hemostasis is confirmed.13 However, some safety concerns have been raised for platelet transfusion in thrombocytopenic patients with CLD, including febrile reactions, allergic or hypersensitivity reactions, hemolysis, infections, graft-versus-host disease, alloimmunization/platelet refractoriness, and failure to achieve the desired increase of platelet counts, in addition to logistical problems such as the need for hospital visits for monitoring, and availability of matched platelets.25

Regarding the efficacy of platelet transfusion for increasing platelet counts, studies have reported that the effect of platelet transfusion in patients with CLD is limited, increasing platelet counts by approximately 10 × 10^9/L.33,34 While in healthy subjects, platelet transfusion increases platelet counts by approximately 30 × 10^9/L.35 A study of platelet transfusion in 26 thrombocytopenic patients with cirrhosis also showed a slight increase in platelet counts.36 A systematic literature review about platelet transfusion found that the efficacy of platelet transfusion varied widely from trial to trial and no clear overall conclusions could be drawn.37 Therefore, there is a need for Japanese consensus guidelines on the optimal combination of TPORAs and platelet transfusion in the treatment for thrombocytopenia in patients with CLD.

EVIDENCE OF THE EFFICACY OF TPORA TREATMENT FOR THROMBOCYTOPENIA IN PATIENTS WITH CLD

Results of TPORA treatment in clinical studies

There is a considerable amount of evidence regarding the efficacy of TPORA treatment for thrombocytopenia in patients with CLD both in Japan and globally. Table 1 shows the results of major clinical trials on lusutrombopag and avatrombopag, which are the currently approved TPORAs in various countries around the world.

Three randomized controlled trials of lusutrombopag for thrombocytopenia in adult patients with CLD showed a significant increase in both the proportion of patients who did not require platelet transfusions prior to undergoing invasive procedures and the response rate (where response was defined as an increase in platelet count of ≥50 × 10^9/L with an increase of ≥20 × 10^9/L from baseline) in the lusutrombopag arm compared with placebo.34,38,39 In addition, it has been reported that independent of baseline values, lusutrombopag for thrombocytopenia in adult patients with CLD increases platelet counts by approximately 1.5-fold and that its platelet-elevating effects are maintained for approximately 3 weeks.40 In an interim analysis of a post-marketing surveillance of lusutrombopag in Japan, preoperative platelet transfusions in patients undergoing invasive procedures were not required in 282 of 300 lusutrombopag-treated patients (94.0%).41 The mean maximum change in platelet count was 41.7 ± 31.4 × 10^9/L. In two randomized controlled trials of avatrombopag for thrombocytopenia in patients with CLD who were planned to undergo invasive procedures, the proportion of patients who did not require preoperative platelet transfusions and the proportion of patients who reached a target
| Study                  | Patients Design | Overall n | Study arm/treatment | n   | Baseline PC, $\times 10^9$/L | Max PC, $\times 10^9$/L | Patient rate without PT, % (n/N) | Responder rate$^{a}$ % (n/N) | Duration of sustained platelet count (>50 $\times 10^9$/L), day | Thrombotic TEAE | Additional information |
|-----------------------|----------------|-----------|---------------------|-----|-----------------------------|--------------------------|---------------------------------|-------------------------------|-------------------------------------------------|---------------|------------------------|
| **Lusutrombopag**     |                |           |                     |     |                             |                          |                                 |                                |                                 |               |                       |
| Phase 3 (L-PLUS 1)    | CLD RCT        | 96        | LUSU                | 48  | 40.9 ± 6.3                  | 87 (59–145)              | 79.2 (38/48)$^{***}$          | 77.1 (37/48)$^{***}$          | 21.09 ± 0.99$^{***}$               | 1             |                       |
|                       |                |           | PBO                 | 48  | 39.9 ± 6.9                  | 52 (29–75)               | 125 (6/48)                     | 6.3 (3/48)                      | 6.05 ± 0.96$^{***}$               |               |                       |
| Phase 3 (L-PLUS 2)    | CLD RCT        | 215       | LUSU                | 108 | 37.7 ± 9.0                  | 85.0                     | 630 (68/108)$^{***}$          | 64.8 (70/108)$^{***}$          | 19.2$^{***}$                       | 2             |                       |
|                       |                |           | PBO                 | 107 | 37.4 ± 7.8                  | 57.5                     | 290 (31/107)                   | 13.1 (14/107)                   | 0.0                                           |               |                       |
| Phase 3 post hoc      | CLD RCT        | 270$^b$   | LUSU                | 137 | 38.6 ± 8.3                  | 89 ± 21 (LUSU without PT) | 737 (101/137)                 | 75.0 (102/136)                  | –                                             | 2             | Max PC = LUSU without PT (n = 101) |
|                       |                |           | PBO                 | 133 | 37.8 ± 7.5                  | 50 ± 13 (PBO with PT)     | 19.5 (26/133)                 | 17.7 (23/130)                   | –                                             | 1             | Max PC = PBO with PT (n = 107)     |
| PMS Sasaki et al.     | CLD Pro        | 331       | LUSU                | 331 | 46.2 ± 13.7                 | 88.7 ± 35.1              | 940 (282/300)                 | –                              | –                                             | Serious AE: 7 | Interim data |
|                       |                |           |                     |     |                             |                          |                                 |                                |                                |                       |                       |
| Phase 2b Tateishi et al. (2019)$^{b,b}$ | CLD RCT | 61 | LUSU 2 mg           | 15  | 40.2 ± 6.4                  | 74, mean                 | 800 (12/15)$^*$               | 66.7 (10/15)                   | 21.22 ± 1.56$^{**}$               | 2             | All patients received RFA        |
|                       |                |           |                     |     |                             |                          |                                 |                                |                                |                       |                       |
|                       |                |           |                     |     |                             |                          |                                 |                                |                                |                       |                       |
|                       |                |           | LUSU 3 mg           | 16  | 41.8 ± 13.2                 | 95, mean                 | 81.3 (13/16)                 | 68.8 (11/16)$^*$               | 21.76 ± 1.66$^{***}$             | 0             |                       |
|                       |                |           | LUSU 4 mg           | 15  | 40.0 ± 7.8                  | 104, mean                | 93.3 (14/15)$^*$              | 80.0 (12/15)$^*$               | 24.23 ± 1.67$^{***}$             | 2             |                       |
|                       |                |           | PBO                 | 15  | 41.8 ± 6.1                  | –                       | 200 (3/15)                    | 6.7 (1/15)                     | 4.33 ± 1.57$^{b}$                | 1             |                       |
| Study                                           | Patients Design | Overall n | Study arm/treatment | n  | Baseline PC, $\times 10^9$/L | Max PC, $\times 10^9$/L | Patient rate without PT, % (n/N) | Responder rate$^a$, % (n/N) | Duration of sustained platelet count ($>50 \times 10^9$/L), day | Thrombotic TEAE | Additional information |
|------------------------------------------------|----------------|-----------|---------------------|----|-----------------------------|-------------------------|----------------------------------|----------------------------|--------------------------------|---------------|-----------------------|
| Phase 3b Numata et al. (2020)$^{31}$          | CLD Open       | 102       | LUSU A/B-1          | 47 | 40.0 (21–53)                | 89.5 (55–173)           | 80.9 (38/47)                    | 83.0 (39/47)                  | 12.8                                         | 1             | A/B: Child–Pugh class A/B. |
|                                                |                |           | LUSU A/B-2          | 47 | 39.0 (24–54)                | 81.0 (59–115)           | 83.0 (39/47)                    | 85.1 (40/47)                  | 13.3                                         | 2             | Discontinuation criteria were applied to A/B-1, not applied to A/B-2. |
|                                                |                |           | LUSU Non-naïve      | 8  | 39.0 (31–47)                | 81.0 (75–98)            | 75.0 (6/8)                      | 75.0 (6/8)                    | 14.3                                         | 0             | Non-naïve: With history of LUSU treatment. |
| Hirooka et al. (2020)$^{43}$                   | CLD Retro      | 144       | LUSU                | 58 | 41.5 (31.8–47.3)            | 81.0 –                | –                                | 70.7 (41/58)                  | –                                            | –             | Responder: PC $\geq 50 \times 10^9$/L |
|                                                |                |           | PT                  | 86 | 42.5 (31.0–50.0)            | –                     | –                                | 5.0 (1/20)                    | –                                            | –             | |
| Takeuchi et al. (2020)$^{65}$                  | CLD Pro        | 80        | LUSU                | 80 | 61 (14–93)                  | $\Delta 49 (-3–301)$ | 97.5 (78/80)                    | 96.3 (77/80)                  | –                                            | 0             | Responder: PC increase $\geq 10 \times 10^9$/L |
| Furuichi et al. (2020)$^{33}$                  | CLD Retro      | 52        | LUSU                | 26 | 45 ± 13                     | $\Delta 48^{**}$       | –                                | 96.1 (25/26)                  | 10$^{**}$                                    | 0             | Propensity score matching. |
|                                                |                |           | PT                  | 26 | 45 ± 15                     | $\Delta 9.5$           | –                                | 15.4 (4/26)                   | 2                                            | 0             | Responder: Increase $>20 \times 10^9$/L |
| Study                  | Patients | Design | Overall n | Study arm/treatment | n     | Baseline PC, $\times 10^9/L$ | Max PC, $\times 10^9/L$ | Patient rate without PT, % (n/N) | Responder rate$^a$, % (n/N) | Duration of sustained platelet count (>50 $\times 10^9/L$), day | Thrombotic TEAE | Additional information |
|------------------------|----------|--------|-----------|---------------------|-------|-----------------------------|------------------------|--------------------------------|-------------------------------|---------------------------------------------------------------|-----------------|----------------------|
| Uojima et al. (2018)$^{66}$ | CLD      | Retro  | 50        | LUSU                | 50    | 44.9 ± 10.3                 | 91.3 ± 35.0           | 96.0 (48/50)                    | 80.0 (40/50)                    | –                                             | 2               |                      |
| Tsuji et al. (2020)$^{67}$    | CLD      | Retro  | 36        | LUSU PC $< 50 \times 10^9/L$ | 11    | 40.5 ± 7.1                  | $\Delta 36 \pm 12$    | 81.8 (9/11)                     | 90.9 (10/11)                     | 16                                             | 0               |                      |
|                           |          |        |           | LUSU PC $\geq 50 \times 10^9/L$ | 25    | 67.7 ± 12.2                 | $\Delta 53 \pm 28$    | 100 (25/25)                    | 100 (25/25)                     | 0                                             |                 |                      |
| Nomoto et al. (2020)$^{68}$    | CLD      | Retro  | 31        | LUSU                | 31    | 39 ± 7                      | $\Delta 31$          | 742 (23/31)                     | 71.0 (22/31)                     | –                                             | 1               | Responder: Increase $>20 \times 10^9/L$ |
| Takada et al. (2019)$^{64}$    | Cirrhosis| Retro  | 153       | LUSU                | 25    | 39 ± 13                     | 82 ± 26               | 840 (21/25)                     | 84.0 (21/25)                     | –                                             | 1               | Without LUSU: With low platelet counts not treated by LUSU |
|                           |          |        |           |                     |       |                             |                       |                                |                               |                                               |                 |                      |
|                           |          |        |           |                      |       |                             |                       |                                |                               |                                               |                 |                      |
|                           |          |        |           |                      |       |                             |                       |                                |                               |                                               |                 |                      |
|                           |          |        |           |                      |       |                             |                       |                                |                               |                                               |                 |                      |
| Kawaratani et al. (2020)$^{62}$ | Cirrhosis| Retro  | 14        | LUSU                | 14    | 55 ± 12                     | 1st $\Delta 23$       | 92.9 (13/14)                    | 92.9 (13/14)                    | –                                             | 1               | Responder: Increase $>20 \times 10^9/L$ |
|                           |          |        |           |                      |       |                             |                       |                                |                               |                                               |                 |                      |
|                           |          |        |           |                      |       |                             |                       |                                |                               |                                               |                 |                      |
|                           |          |        |           |                      |       |                             |                       |                                |                               |                                               |                 |                      |
| Sano et al. (2021)$^{64}$     | CLD      | Retro  | 8         | LUSU                | 8     | 44 (35–49)                  | 1st $\Delta 46.0$     | 1st 100 (8/8)                    | 1st 100 (8/8)                    | –                                             | 0               |                      |
|                           |          |        |           |                      |       |                             |                       |                                |                               |                                               |                 |                      |
|                           |          |        |           |                      |       |                             |                       |                                |                               |                                               |                 |                      |
|                           |          |        |           |                      |       |                             |                       |                                |                               |                                               |                 |                      |
|                           |          |        |           |                      |       |                             |                       |                                |                               |                                               |                 |                      |
| Study                        | Patients | Design | Overall n | Study arm/treatment n | Baseline PC, $\times 10^9$/L | Max PC, $\times 10^9$/L | Patient rate without PT, % (n/N) | Responder rate$^a$, % (n/N) | Duration of sustained platelet count (>50 $\times 10^9$/L), day | Thrombotic TEAE | Additional information                      |
|-----------------------------|----------|--------|-----------|-----------------------|-------------------------------|--------------------------|---------------------------------|-----------------------------|------------------------------------------------|-------------|---------------------------------------------|
| Ishikawa et al. (2019)$^{63}$ | HCC Retro 8 LUSU | 8      | 8         | 42.7 ± 5.2            | 111 ± 18                     | 100 (8/8)                | –                               | –                           | –                                           | 0           | 1 non-TEAE of portal vein thrombosis in the AVA group |
| **Avatrombopag**            |          |        |           |                       |                              |                          |                                 |                             |                                              |             |                              |
| Phase 3 (ADAPT-1, ADAPT-2)  | CLD RCT 435 | ADAPT-1 $<40 \times 10^9$/L AVA | 90    | 31 ± 7               | $\Delta 32^{***}$            | 65.6 (59/90)$^{***}$     | 68.9 (62/90)$^{***}$            | –                           | 0                                           |             | 1 non-TEAE of portal vein thrombosis in the AVA group |
| Terrault et al. (2018)$^{42}$ |          |        |           |                       |                              |                          |                                 |                             |                                              |             |                              |
| ADAPT-1 $<40 \times 10^9$/L PBO | 48      | 31 ± 7 | $\Delta 0.8$ | 229 (11/48)           | 4.2 (2/48)                  | –                         | 0                               |                             |                                              |             |                              |
| ADAPT-1 40–$<50 \times 10^9$/L AVA | 59    | 44 ± 3 | $\Delta 37.1^{***}$ | 88.1 (52/59)$^{***}$     | 88.1 (52/59)$^{***}$         | –                         | 0                               |                             |                                              |             |                              |
| ADAPT-1 40–$<50 \times 10^9$/L PBO | 34    | 45 ± 3 | $\Delta 1.0$  | 38.2 (13/34)          | 20.6 (7/34)                 | –                         | 0                               |                             |                                              |             |                              |
| ADAPT-2 $<40 \times 10^9$/L AVA | 70    | 33 ± 5 | $\Delta 31.3^{***}$ | 68.6 (48/70)$^*$         | 67.1 (47/70)$^{***}$          | –                         | 0                               |                             |                                              |             |                              |
| ADAPT-2 $<40 \times 10^9$/L PBO | 43    | 33 ± 6 | $\Delta 3.0$  | 349 (15/43)           | 7.0 (3/43)                  | –                         | 0                               |                             |                                              |             |                              |
| ADAPT-2 40–$<50 \times 10^9$/L AVA | 58    | 44 ± 4 | $\Delta 44.9^{***}$ | 87.9 (51/58)$^{***}$     | 93.1 (54/58)$^{***}$         | –                         | 1                               |                             |                                              |             |                              |
| ADAPT-2 40–$<50 \times 10^9$/L PBO | 33    | 45 ± 3 | $\Delta 5.9$  | 333 (11/33)           | 39.4 (13/33)                | –                         | 2                               |                             |                                              |             |                              |

(Continues)
| Study Design | Overall | Study arm/treatment | n | Baseline PC, $\times 10^9$/L | Max PC, $\times 10^9$/L | Patient rate without PT, % (n/N) | Responder rate $^a$ % (n/N) | Duration of sustained platelet count ($>50 \times 10^9$/L), day | Thrombotic TEAE | Additional information |
|-------------|---------|---------------------|---|----------------------------|-------------------------|---------------------------------|-----------------------------|---------------------------------|----------------|----------------------|
| Phase 2 Terrault et al. (2014) CLD RCT 93 | AVA-A 100/20 mg | 18 | 40.0 (18–55) | 78 | 86.3 (44/51) | 38.9 (7/18) | 0 | 100 mg AVA loading dose followed by 20, 40, or 80 mg/day on days 2–7 |
| | AVA-A 100/40 mg | 16 | 82 | 31.3 (5/16) | - | - | 0 |
| | AVA-A 100/80 mg | 17 | 105 | 76.5 (13/17)$^{**}$ | - | - | 0 |
| | PBO-A | 16 | 38.0 (18–52) | 49 | 100 (16/16) | 6.3 (1/16) | - | 0 |
| | AVA-B 80/10 mg (for days 2–7) | 21 | 42.0 (18–57) | 74 | 95.2 (40/42) | 42.9 (9/21) | - | 0 |
| | AVA-B 80/20 mg (for days 2–4) | 21 | 69 | 52.4 (11/21) | - | - | 0 |
| | PBO-B | 21 | 38 (20–55) | 47 | 66.7 (14/21) | 9.5 (2/21) | - | 0 |

Note: Data are shown as % (n/N) or median (range), mean ± standard deviation unless otherwise indicated. $^a$p < 0.001 versus PBO; $^b$p < 0.001 versus platelet transfusion; $^{**}$p < 0.0001 versus PBO.

Abbreviations: ADR, adverse drug reaction; AE, adverse event; AVA, avatrombopag; CLD, chronic liver disease; HCC, hepatocellular carcinoma; LUSU, lusutrombopag; Max, maximum; PBO, placebo; PC, platelet count; PMS, post-marketing surveillance; Pro, prospective; PT, platelet transfusion; RCT, randomized controlled trial; Retro, retrospective; RFA, radiofrequency ablation; TEAE, treatment-emergent adverse event; $\Delta$, change.

$^a$Defined as having a platelet count of $\geq 50 \times 10^9$/L (and an increase of $\geq 20 \times 10^9$/L from baseline at any time).

$^b$Per-protocol.
platelet count of $\geq 50 \times 10^9/L$ on the day of the procedure were significantly higher in the avatrombopag arm compared with the placebo arm.\textsuperscript{42}

On the other hand, it has also been reported that the efficacy of lusutrombopag depends on the severity of thrombocytopenia, spleen size, and other factors. In patients with a baseline platelet count of $<30 \times 10^9/L$, lusutrombopag may not be as effective in achieving a target platelet count of $\geq 50 \times 10^9/L$ compared with patients with less severe thrombocytopenia.\textsuperscript{43} However, in another study that considered both platelet count and splenic volume combined, among patients with platelet count $\leq 30 \times 10^9/L$ before lusutrombopag treatment, no patients with a splenic volume below the threshold required platelet transfusion, while all patients with a splenic volume above the threshold required platelet transfusion, suggesting that the baseline platelet count may affect the efficacy of lusutrombopag when the spleen is enlarged.\textsuperscript{44} Conversely, data from a phase 3 study in Japan demonstrated that lusutrombopag increased platelet counts regardless of splenic volume and platelet count recovery was not significantly correlated with splenic volume.\textsuperscript{34} Thus, the effect of pre-dose platelet count and splenic volume on the efficacy of lusutrombopag warrants further study.

Thrombotic events during TPORA treatment

As the balance between pro- and anticoagulation factors is unstable in patients with cirrhosis, the risk of venous thromboembolism is two-fold higher in these patients versus those without liver disease.\textsuperscript{22} Therefore, thrombosis-related adverse events with the use of TPORAs are of clinical interest.

In a phase 3 study in Japan (L-PLUS 1), two patients, one in the lusutrombopag arm and one in the placebo arm, had a thrombosis-related adverse event.\textsuperscript{34} The event in the lusutrombopag arm was portal vein thrombosis (PVT) and was considered as possibly related
to lusutrombopag treatment. In a global phase 3 study of lusutrombopag (L-PLUS 2), there were four thrombosis-related adverse events, two in the lusutrombopag arm and two in the placebo arm, but the two events in the lusutrombopag arm were not considered to be related to the study drug.\textsuperscript{38} In a post-marketing surveillance of lusutrombopag in Japan, PVT was observed in six cases (1.81%), of which four cases (1.21%) were determined to be related to lusutrombopag.\textsuperscript{41} In a global phase 3 study of avatrombopag (ADAPT-2), three patients had a thrombosis-related adverse event in the high baseline platelet count cohort.\textsuperscript{42} One patient in the avatrombopag arm presented with PVT and two patients in the placebo arm presented with acute myocardial infarction, disseminated intravascular coagulation, and pulmonary embolism. Two meta-analyses of TPORAs showed no significant difference in the frequency of PVT or thrombotic events with lusutrombopag or avatrombopag compared with placebo.\textsuperscript{26,45} Nevertheless, thrombosis has been reported even in patients with below-normal platelet counts, and because thrombosis may occur following an invasive procedure, particularly in patients with a history of thrombosis or thromboembolism, all patients should be closely monitored following TPORA administration, as indicated in the package inserts.\textsuperscript{18,46-49}

**Hemorrhagic events during TPORA treatment**

Although TPORAs for the treatment of thrombocytopenia aim to reduce the risk of hemorrhagic complications in patients with CLD, it is difficult to verify whether TPORAs significantly suppress the incidence of bleeding events. The reason it is difficult to obtain clear evidence on this is that the incidence rate of bleeding events has not been established as an endpoint in trials on TPORAs and the invasive procedures, as well as the patient characteristics, vary.

In a post hoc safety analysis that included pooled data from three clinical trials on lusutrombopag, the incidences of bleeding events in the lusutrombopag and placebo arms were 6.5% and 11.9%, respectively.\textsuperscript{50} In two global phase 3 studies of avatrombopag (ADAPT-1 and ADAPT-2), the incidences of bleeding events (World Health Organization Grade ≥2) in the avatrombopag and placebo arms were 3.8% and 3.3% in the low baseline platelet count cohort and 2.6% and 4.6% in the high baseline platelet count cohort, respectively.\textsuperscript{42} A meta-analysis of TPORAs showed that the incidence of the periprocedural bleeding events significantly decreased in the TPORA arm versus the placebo arm in thrombocytopenic patients with CLD without increasing the rate of thrombosis.\textsuperscript{26} Therefore, the use of TPORAs may be considered as an alternative to platelet transfusion in the treatment of thrombocytopenia in patients with CLD.

**T A B L E 2**

| Bleeding risk | Invasive procedure |
|---------------|--------------------|
| Moderate      | Radiofrequency ablation |
|               | Endoscopic injection sclerotherapy |
|               | Endoscopic submucosal dissection |
|               | Endoscopic mucosal resection |
|               | Liver biopsy\textsuperscript{b} |
| Mild          | Transcatheter arterial chemoembolization |
|               | Endoscopic variceal ligation |
|               | Any other procedures not classified as “moderate” |

\textsuperscript{a}Defined according to the consensus reached during the expert panel meetings on February 20, 2021 and March 15, 2021.

\textsuperscript{b}Because this is a diagnostic test, the risk of bleeding should be minimized.

**TREATMENT ALGORITHM FOR THROMBOCYTOPENIA IN PATIENTS WITH CLD**

**Treatment decision based on the risk of invasive procedures and platelet count**

Considering the recent evidence of TPORA treatment mentioned above, an expert panel was convened to examine the data, with the aim of proposing a treatment algorithm for thrombocytopenia in patients with CLD. The resulting algorithm targets patients with thrombocytopenia and CLD whose platelet count is \(<150 \times 10^9/L\) and who are eligible for platelet transfusion (Figure 1).

The first decision step is that platelet transfusion should be considered for patients with CLD who are planned to undergo invasive procedures with high bleeding risk (major surgeries such as open abdominal surgery, open chest surgery, open-heart surgery, craniotomy procedure, and evisceration) or patients with severe liver dysfunction (Child–Pugh class C). In fact, platelet transfusion should be considered in patients with severe liver dysfunction (Child–Pugh class C) who are planned to undergo major surgery because lusutrombopag is contraindicated in these cases based on the Japanese package insert.\textsuperscript{18} Next, the algorithm provides optimal treatment options for thrombocytopenia in patients with CLD who were planned to undergo diagnostic or therapeutic procedures not considered as major surgery, including non-gastroenterological procedures, based on the pretreatment platelet count and the bleeding risk of the invasive procedure. Four cut-off values for pretreatment platelet count were set at \(<50 \times 10^9/L\), \(50–<75 \times 10^9/L\), \(75–<100 \times 10^9/L\), and \(\geq 100 \times 10^9/L\) (Figure 1). While some of these values have been defined previously,\textsuperscript{16,17} our algorithm is the first to specifically include these four cut-off values. By providing specific treatment
options for each of the four different pretreatment platelet count categories, optimal use of platelet products can be achieved. Among the resulting patient groups, those with severe thrombocytopenia (platelet count \(<50 \times 10^9/L\) and CLD should be treated to restore the platelet count to \(\geq 50 \times 10^9/L\) prior to invasive procedures. The cut-off value for platelet transfusion in patients planned to undergo invasive procedures is set at \(<50 \times 10^9/L\) in domestic and international guidelines.\(^5\)\(^-\)\(^13\)

In a retrospective study of 874 patients with cirrhosis who underwent invasive procedures, patients with platelet counts \(\leq 50 \times 10^9/L\) had a higher frequency of major bleeding than those who did not (4.9% vs. 1.6%, \(p = 0.008\)).\(^1\) The HALT-C trial, which examined case report forms from 2740 liver biopsies, also found an increased risk of bleeding for patients undergoing percutaneous liver biopsy with platelet counts \(<60 \times 10^9/L\) versus \(\geq 60 \times 10^9/L\).\(^2\) Another study found that among 50 patients undergoing an invasive procedure during evaluation for potential liver transplantation, 31% of patients with severe thrombocytopenia (platelet count \(<75 \times 10^9/L\) experienced a bleeding event, whereas none of the patients with moderate thrombocytopenia experienced bleeding.\(^3\) Conversely, several studies have reported no direct relationship between platelet count and bleeding risk during invasive procedures in patients with CLD. In a prospective analysis of 852 procedures carried out in 363 patients with cirrhosis who were planned to undergo invasive procedures, post-procedural bleeding was not predictable based on baseline platelet count and PT-INR.\(^4\) In a prospective analysis of 280 patients with cirrhosis, there was no significant difference in platelet count between patients who experienced major bleeding and those who did not after an invasive procedure.\(^5\) A recent narrative review concluded that there is still a lack of adequate and reliable data describing the risk of bleeding following invasive procedures in patients with advanced liver disease, and its potential association with decreased platelet count.\(^6\)

**Treatment options for patients with platelet count \(<50 \times 10^9/L\)**

For patients with CLD whose pretreatment platelet count is \(<50 \times 10^9/L\), our algorithm recommends TPORAs as first-line therapy (Figure 1). For patients who are ineligible for treatment with TPORAs, such as children and pregnant women, or patients who require urgent procedures, platelet transfusion can be considered. As the platelet-increasing efficacy of lusutrombopag is maintained for approximately 3 weeks,\(^34\)\(^,\)\(^40\) in principle, a single cycle of TPORA treatment should be administered per planned invasive procedure.\(^18\)

Based on the efficacy and safety results of recent studies of TPORAs (Table 1) and a meta-analysis,\(^26\) we determined that TPORAs are appropriate as first-line treatment. The 2020 Guideline for the Treatment of Cirrhosis in Japan also strongly recommends the use of TPORAs for the treatment of thrombocytopenia in patients with cirrhosis who are scheduled to undergo planned invasive procedures.\(^7\)

Our algorithm provides the choice of subsequent therapy based on the degree of recovery of platelet count using the following three categories: \(<50 \times 10^9/L\), \(50 \leq \leq 75 \times 10^9/L\), and \(\geq 75 \times 10^9/L\) (Figure 1). If the platelet count remains \(<50 \times 10^9/L\) in patients treated with TPORAs, platelet transfusion should also be considered. However, it has been reported that platelet transfusion in patients treated with lusutrombopag did not result in an apparent increase in platelet count,\(^24\) and therefore, further evidence is required.

In patients with a pretreatment platelet count of \(<50 \times 10^9/L\) if the platelet count increases to \(50 \leq \leq 75 \times 10^9/L\) after TPORA treatment, our algorithm provides a therapeutic strategy according to whether the planned invasive procedure has a moderate or mild bleeding risk, with additional platelet transfusion to be considered when the risk is moderate. Invasive procedures with moderate bleeding risk include radiofrequency ablation, endoscopic injection sclerotherapy, endoscopic submucosal dissection, endoscopic mucosal resection, and liver biopsy (Table 2).

If the planned invasive procedure has a mild bleeding risk, the procedure can be performed without further therapeutic intervention. Invasive procedures with mild bleeding risk include transcatheter arterial chemoembolization, endoscopic variceal ligation, and any other invasive procedure not specified as having “moderate” risk (Table 2). If the platelet count is \(\geq 75 \times 10^9/L\) after TPORA treatment, according to our algorithm, the patient is considered eligible to undergo the invasive procedure without further therapeutic intervention.

Of note, according to our algorithm, patients with a pretreatment platelet count of \(75 \leq \leq 100 \times 10^9/L\) are considered eligible for the invasive procedure without any therapeutic intervention; nonetheless, TPORA treatment should be considered as necessary on a case-by-case basis. However, in patients with a pretreatment platelet count of \(<50 \times 10^9/L\) if the platelet count recovers to \(\geq 75 \times 10^9/L\) after TPORA treatment, our algorithm considers that the patient is eligible for the invasive procedure without further therapeutic intervention, because the patient has already been treated with TPORAs and no longer meets the criteria for platelet transfusion.

**Indications for splenectomy or partial splenic embolization**

For patients planned for multiple invasive procedures, according to our algorithm, splenectomy or partial splenic embolization (PSE) should be considered (Figure 1 [see footnote h]). Splenectomy is commonly performed by laparotomy or laparoscopic operation. The outcomes of patients with cirrhosis undergoing laparoscopic splenectomy, which is a less invasive technique than laparotomy, have been reported from a prospective surgical study with accompanying chart review.\(^57\) The study authors reported that all 28 consecutive patients with cirrhosis and thrombocytopenia who underwent
sive procedure one cycle of TPORA treatment should be administered per inva-
penia is required before another invasive procedure. In principle, should be considered instead when treatment for thrombocyto-
with CLD who have inadequate increase of platelet count after
initial TPORA treatment, platelet transfusion or splenectomy/PSE
should be considered (Figure 1 [see footnote g]). However, for patients
planned to undergo a second or subsequent invasive procedure. In principle.

Retreatment with TPORAs

If a patient with increased platelet count after the first TPORA
treatment is planned to undergo a second or subsequent invasive
procedure, according to our algorithm, TPORA retreatment should
be considered in patients with CLD who have inadequate increase of platelet count after
initial TPORA treatment. However, for patients
\[\text{retreatment should be considered.}\]

There have been several studies in recent years on the efficacy of lusutrombopag retreatment for thrombocytopenia in patients with CLD who are planned to undergo another invasive procedure after TPORA treatment for the initial invasive procedure. In an interim analysis of a post-marketing surveillance of lusutrombopag, patients who received repeated cycles of lusutrombopag (2 cycles, 20 patients; 3 cycles, 1 patient) all showed an increase in platelet count similar to that achieved with the first
dose. In a phase 3b study of lusutrombopag in patients with Child–Pugh class A or B CLD, patients receiving a second cycle of lusutrombopag (n = 8) had increased platelet counts similar to those of patients receiving the first cycle (n = 94). In a study of lusutrombopag in 14 patients with cirrhosis, there was no significant difference in the rate of platelet count increase between the first, second, and third or later treatment cycles (p = 0.87).

Other studies on repeated lusutrombopag treatment in a small number of patients have reported an increase in the platelet count after the second treatment cycle that was similar to that after the first treatment cycle.

Treatment options for patients with platelet count of 50–<75 \times 10^9/L

According to our algorithm, for patients with thrombocytopenia and CLD whose pretreatment platelet count is 50–<75 \times 10^9/L and who are planned to undergo an invasive procedure with moderate bleeding risk, TPORA treatment should be considered. In such cases, a target platelet count of \geq 75 \times 10^9/L is recommended (Figure 1 [see footnote c]). There is some evidence that platelet counts \text{<75} \times 10^9/L may increase the risk of bleeding in patients undergoing invasive procedures with moderate bleeding risk. A study comparing bleeding events after orthotopic liver transplantation in 50 patients with cirrhosis and thrombocytopenia reported that the events were more frequent in patients with platelet counts \text{<75} \times 10^9/L and no events were observed in patients with platelet counts \geq 75 \times 10^9/L. According to our algorithm, a platelet count of \text{\geq 75} \times 10^9/L, which is often used as a standard cut-off in clinical practice, is recommended when planned procedures have a moderate bleeding risk, such as radiofrequency ablation, endoscopic injection sclerotherapy, endoscopic submucosal dissection, and endoscopic mucosal resection.

Evidence for the efficacy of TPORA treatment for moderate thrombocytopenia in patients with CLD has also been reported in recent years (Table 1). In a post-marketing surveillance of lusutrombopag for thrombocytopenia, the platelet count increased in patients with pretreatment platelet counts \text{\geq 50} \times 10^9/L was similar to that in patients with pretreatment platelet counts \text{<50} \times 10^9/L. A retrospective study of lusutrombopag in patients with CLD also showed comparable efficacy in patients with baseline platelet counts \text{\geq 50} \times 10^9/L and \text{<50} \times 10^9/L.

Treatment options for patients with platelet count of 75–<100 \times 10^9/L

For patients with a pretreatment platelet count of 75–<100 \times 10^9/L, our algorithm recommends treatment with TPORAs or other therapies at the physician’s discretion (Figure 1 [footnote b]). Among the procedures with moderate bleeding risk (Table 2), liver biopsy differs from the other procedures because it is a diagnostic test and the bleeding risk should be minimized. Because it is necessary to avoid therapeutic hesitancy, it is not strictly necessary for patients to achieve a platelet count of \text{\geq 100} \times 10^9/L prior to liver biopsy. However, it was suggested in the panel discussion that TPORA treatment should be an available option to reduce risk of bleeding for patients with platelet counts of 75–<100 \times 10^9/L, with a target platelet count of \text{\geq 100} \times 10^9/L.

Bleeding complications associated with liver biopsy have been reported. In a post hoc analysis of the trial of 2740 patients with cirrhosis associated with hepatitis C who underwent liver biopsy (the HALT-C trial), the overall incidence of bleeding complications was 0.6% and the incidence increased to 5.3% in the patients with platelet count \text{\leq 60} \times 10^9/L. The analysis also showed that the incidence of
bleeding complications was 0.4% in patients with an INR of ≤1.1, but it increased to 2.4% in those with an INR of ≥1.3. Thus, a decision to proceed with TPORA treatment prior to liver biopsy should be made by the attending physician after considering the patient’s condition and bleeding risk (e.g., based on their platelet count, PT-INR, and liver function).

Treatment options for patients with platelet count of ≥100 × 10^9/L

According to our algorithm, patients with CLD whose platelet count is ≥100 × 10^9/L are eligible for invasive procedures without the need for TPORA treatment or other therapies. We found little published evidence of bleeding risk evaluation in patients with CLD whose platelet count was 100–150 × 10^9/L. A single post hoc analysis of the HALT-C trial showed that the bleeding frequency in the platelet count range of 101 × 10^9/L–150 × 10^9/L was 0.7%, which was low compared with other platelet count ranges evaluated (e.g., a frequency of 5.3% in patients with a platelet count ≤60 × 10^9/L). Therefore, our algorithm considers these patients eligible for invasive procedures without TPORA treatment or other therapies.

CLOSING REMARKS

Because thrombocytopenia is highly prevalent in patients with CLD, it is necessary to reduce bleeding risk during diagnostic or therapeutic procedures. In Japan, there are no specific guidelines for platelet transfusion and TPORA treatment in this patient population, and no nationwide treatment consensus exists. To date, patients with CLD and thrombocytopenia in Japan have generally been treated with platelet transfusion or TPORAs at the discretion of the attending physician based on their experience. Considering the current situation in Japan, where there is a shortage of blood products and plasma derivatives, proper use of these blood supplies is essential. Therefore, we developed an algorithm based on the consensus of experts who discussed the latest evidence on TPORA treatment and platelet transfusion for thrombocytopenia. In Japan, the TPORA lusutrombopag has been used in clinical practice, and its efficacy and safety under various conditions was compared with that of platelet transfusion. After considering the resultant data, we developed our algorithm, which is expected to be a clinically useful guideline for the management of thrombocytopenia in patients with CLD. This algorithm will contribute to the optimal management of thrombocytopenia in CLD patients in Japan, as the need for the use of TPORAs is expected to increase in the future, given the short supply of platelet products. Furthermore, we hope that our algorithm may be useful for the optimal treatment of thrombocytopenia in other countries with a healthcare situation comparable with that of Japan.

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CONFLICT OF INTEREST

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REFERENCES

1. Hancox SH, Smith BC. Liver disease as a cause of thrombocytopenia. J QJM. 2013;106:425–31.
2. Peck-Radosavljevic M. Thrombocytopenia in chronic liver disease. Liver Int. 2017;37:778–93.
3. Van Dievoet MA, Eeckhoudt S, Stephenne X. Primary hemostasis in chronic liver disease and cirrhosis: what did we learn over the past decade? Int J Mol Sci. 2020;21:3294.
4. Qamar AA, Grace ND, Grozmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK, et al. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. Clin Gastroenterol Hepatol. 2009;7:689–95.
5. Miller JB, Figueroa EJ, Haug RM, Shah NL. Thrombocytopenia in chronic liver disease and the role of thrombopoietin agonists. Gastroenterol Hepatol. 2019;15:326–32.
6. Escourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP, et al. Guidelines for the use of platelet transfusions. Br J Haematol. 2017;176:365–94.
7. Yoshiji H, Nagoshi S, Akahane T, Asaoka Y, Ueno Y, Ogawa K, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2020. J Gastroenterol. 2021;56:593–619.
8. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinnmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2015;162:205–13.
9. Neuberger J, Patel J, Caldwell H, Davies S, Hebdtich V, Hollywood C, et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. Gut. 2020;69:1382–403.
10. O’Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA clinical practice update: coagulation in cirrhosis. Gastroenterology. 2019;157:34–43.
11. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology. 2009;49:1017–44.
12. Shiba G, Ibrahim A, Helmy A, Sarin SK, Omata M, Kumar A, et al. Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis: a 2016 update. Hepatol Int. 2017;11:1–30.
13. Takami A, Matsushita T, Ogata M, Fujii N, Kubuki Y, Fujiwara S, et al. Guideline for the use of platelet transfusion concentrates based on scientific evidence: update 2019. Japanese J Transfus Cell Ther. 2019;65:544–61.

14. Brown RS, Jr. Current management of thrombocytopenia in chronic liver disease. Gastroenterol Hepatol. 2019;15:15–7.

15. Dieterich DT, Bernstein D, Flamm S, Pockros PJ, Reau N. Review article: a treatment algorithm for patients with chronic liver disease and severe thrombocytopenia undergoing elective medical procedures in the United States. Aliment Pharmacol Ther. 2020;52:1311–22.

16. Saab S, Bernstein D, Hassanein T, Kugelmans M, Kwo P. Treatment options for thrombocytopenia in patients with chronic liver disease undergoing a scheduled procedure. J Clin Gastroenterol. 2020;54:503–11.

17. Saab S, Brown RS, Jr. Management of thrombocytopenia in patients with chronic liver disease. Dig Dis Sci. 2019;64:2757–68.

18. Shionogi & Co, Ltd Lusutrombopag (Mulpleta®) package insert. https://www.info.pmda.go.jp/go/pack/3399010F1022_1_03/ (2019). Accessed 1 Jun 2021.

19. The Japan Society of Transfusion Medicine and Cell Therapy. Urgent recommendations for the shortage of blood products due to the pandemic of COVID-19 infection. https://www.jaam.jp/info/2020/files-info-20200421_2.pdf (2020). Accessed 1 Jun 2021.

20. Hayashi H, Beppu T, Shirabe K, Maehara Y, Baba H. Management of thrombocytopenia due to liver cirrhosis: a review. World J Gastroenterol. 2014;20:2595–605.

21. Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, et al. Thrombopoiitin receptor agonist is more effective than platelet transfusion for treating thrombocytopenia in adults with chronic liver disease. Hepatology. 2015;62:1062–70.

22. Tripodi A. Hemostasis abnormalities in cirrhosis. Curr Opin Hematol. 2008;15:705–18.

23. Zermatten MG, Fraga M, Moradpour D, Bertaggia Calderara D, Samkari H, Jou JH, McCarty OJT, et al. Role of severe thrombocytopenia in preventing platelet count recovery in thrombocytopenic patients with chronic liver disease. J Gastroenterol Hepatol. 2020;35:299–304.

24. Takada H, Kurosaki M, Nakanishi H, Takahashi Y, Itakura J, Tsuchiya T, et al. Randomized controlled trial of lusutrombopag in Japanese patients with chronic liver disease undergoing radiofrequency ablation. J Gastroenterol. 2019;54:171–81.

25. Terrault N, Chen YC, Izumi N, Kayali Z, Mitrut P, Tak WY, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. Gastroenterology. 2018;155:705–18.

26. Lusutrombopag reduces need for platelet transfusion in patients with thrombocytopenia undergoing invasive procedures. C Gin Gastroenterol Hepatol. 2019;17:1192–200.

27. Furuichi Y, Takeuchi H, Yoshimasu Y, Kasai Y, Abe M, Ito T. Thrombopoietin receptor agonist is more effective than platelet transfusion for chronic liver disease with thrombocytopenia, shown by propensity score matching. Hepatol Res. 2020;50:1062–70.

28. Newland A, Bentley R, Jakubowska A, Liebman H, Lorenz J, Peck-Radosavljevic M, et al. A systematic literature review on the use of platelet transfusions in patients with thrombocytopenia. Hema- tology. 2019;24:679–719.

29. Leclercq V, Vanderschueren M, Vandeputte N, Philip P, Rousset F, et al. Assessment of time to platelet count increase in response to lusutrombopag. JHEP Rep. 2021;3:100228.

30. European Medicines Agency. Mulpleo 3 mg film-coated tablets: full prescribing information. https://www.ema.europa.eu/en/medicines/human/EPAR/mulpleo (2018). Accessed 10 Aug 2021.

31. European Medicines Agency, Mulpleo 3 mg film-coated tablets: summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/mulpleoepar-product-information_en.pdf (2019). Accessed 10 Aug 2021.

32. Blumberg N, Heal JM, Phillips GL. Platelet transfusions: trigger, dose, benefits, and risks. F1000 Med Rep. 2010;2:5.
50. Giannini EG, Kano T, Ochiai T, Bentley R, Shrestha P, Afdhal N. Bleeding events in lusutrombopag-treated thrombocytopenic patients. Eur J Clin Invest. 2021;51:e13503.

51. Li J, Han B, Li H, Deng H, Méndez-Sánchez N, Guo X, et al. Association of coagulopathy with the risk of bleeding after invasive procedures in liver cirrhosis. Saudi J Gastroenterol. 2018;24:220–7.

52. Seeff LB, Everson GT, Morgan TR, Curto TM, Lee WM, Ghany MG, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol. 2010;8:877–83.

53. Giannini EG, Greco A, Marenco S, Andorno E, Valente U, Savarino V. Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. Clin Gastroenterol Hepatol. 2010;8:899–902.

54. Napolitano G, Iacobellis A, Merla A, Niro G, Valvano MR, Terracciano F, et al. Bleeding after invasive procedures is rare and unpredicted by platelet counts in cirrhotic patients with thrombocytopenia. Eur J Intern Med. 2017;38:79–82.

55. Basil S, Raparelli V, Napoleone I, Talerico G, Corazza GR, Perticone F, et al. Platelet count does not predict bleeding in cirrhotic patients: results from the PRO-LIVER study. Am J Gastroenterol. 2018;113:368–75.

56. Alvaro D, Caporaso N, Giannini EG, Iacobellis A, Morelli M, Toniotto P, et al. Procedure-related bleeding risk in patients with cirrhosis and severe thrombocytopenia. Eur J Clin Invest. 2021;51:e13508.

57. Kakinoki K, Okano K, Suto H, Oshima M, Hagiike M, Usuki H, et al. Hand-assisted laparoscopic splenectomy for thrombocytopenia in patients with cirrhosis. Surg Today. 2013;43:883–8.

58. Hayashi H, Beppu T, Masuda T, Mizumoto T, Takahashi M, Ishiko T, et al. Predictive factors for platelet increase after partial splenic embolization in liver cirrhosis patients. J Gastroenterol Hepatol. 2007;22:1638–42.

59. Hayashi H, Beppu T, Okabe K, Masuda T, Okabe H, Baba H. Risk factors for complications after partial splenic embolization for liver cirrhosis. Br J Surg. 2008;95:744–50.

60. Cai M, Huang W, Lin C, Li Z, Qian J, Huang M, et al. Partial splenic embolization for thrombocytopenia in liver cirrhosis: predictive factors for platelet increment and risk factors for major complications. Eur Radiol. 2016;26:370–80.

61. Numata K, Tanaka K, Katsube T, Ochiai T, Fukuhara T, Kano T, et al. Is platelet monitoring during 7-day lusutrombopag treatment necessary in chronic liver disease patients with thrombocytopenia undergoing planned invasive procedures? A phase IIIb open-label study. Hepatol Res. 2020;50:1141–50.

62. Kawaratani H, Tsuji Y, Ishida K, Kaya D, Kubo T, Fujinaga Y, et al. Effect of three or more treatments with lusutrombopag in patients with cirrhotic thrombocytopenia: a retrospective single-center study. Hepatol Res. 2020;50:1101–5.

63. Ishikawa H, Oshimi T, Tomiyoshi K, Kojima Y, Horigome R, Imai M, et al. Efficacy and safety of repeated use of lusutrombopag prior to radiofrequency ablation in patients with recurrent hepatocellular carcinoma and thrombocytopenia. Hepatol Res. 2019;49:590–3.

64. Sano Y, Morimoto M, Kobayashi S, Ueno M, Fukushima T, Asama H, et al. Repeated lusutrombopag treatment for thrombocytopenia in patients with chronic liver disease. Digestion. 2021;102:654–62.

65. Takeuchi H, Furuichi Y, Yoshimasu Y, Kasai Y, Abe M, Sugimoto K, et al. The thrombopoietin receptor agonist lusutrombopag is effective for patients with chronic liver disease and impaired renal function. J Nippon Med Sch. 2020;87:325–33.

66. Uojima H, Arase Y, Itokawa N, Atsukawa T, Satoh T, Miyazaki K, et al. Relationship between response to lusutrombopag and splenic volume. World J Gastroenterol. 2018;24:5271–9.

67. Tsuji Y, Kawaratani H, Ishida K, Kaya D, Kubo T, Fujinaga Y, et al. Effectiveness of lusutrombopag in patients with mild to moderate thrombocytopenia. Dig Dis. 2020;38:329–34.

68. Nomoto H, Morimoto N, Miura K, Watanabe S, Takaoka Y, Maeda H, et al. Lusutrombopag is effective and safe in patients with chronic liver disease and severe thrombocytopenia: a multicenter retrospective study. BMC Gastroenterol. 2020;20:427.

69. Terrault NA, Hassanein T, Howell CD, Joshi S, Lake J, Sher L, et al. Phase II study of avatrombopag in thrombocytopenic patients with cirrhosis undergoing an elective procedure. J Hepatol. 2014;61:1253–9.