Abstract:

Objective Lusutrombopag is a thrombopoietin receptor agonist that improves thrombocytopenia in patients with chronic liver disease scheduled to undergo invasive procedures. However, information on the efficacy of repeated lusutrombopag treatment and factors associated with the treatment is scarce. We analyzed the efficacy of repeated lusutrombopag treatment and the factors associated with a response to lusutrombopag.

Methods Thirty-nine patients with chronic liver disease who received lusutrombopag treatment before undergoing invasive procedures were enrolled in this retrospective study. Of the 39 patients, 10 received lusutrombopag treatment multiple times for a total of 53 regimens of lusutrombopag treatment. Changes in platelet counts, the effects of repeated lusutrombopag treatment, and factors associated with response to lusutrombopag were analyzed.

Results The median platelet count increased significantly from $4.5 \times 10^4/\mu L$ before lusutrombopag treatment to $7.2 \times 10^4/\mu L$ before the invasive procedure (p<0.01), and patients undergoing 49 of the 53 (92%) treatment regimens succeeded in undergoing invasive procedures without needing platelet transfusions. In patients who received lusutrombopag treatment repeatedly, the median platelet count significantly increased following the second administration of lusutrombopag, and the effects of lusutrombopag were similar between the first and second administration. A multivariate analysis identified the absence of diabetes mellitus (odds ratio, 5.56 for presence; p=0.04) as a significant and independent predictor of a response to lusutrombopag.

Conclusion Lusutrombopag treatment significantly increased platelet counts in patients with chronic liver disease, making it possible to receive invasive procedures. The treatment produced identical effects when it was repeated. The efficacy of lusutrombopag might be decreased in patients with diabetes mellitus.

Key words: lusutrombopag, thrombocytopenia, thrombopoietin receptor agonist, chronic liver disease, diabetes mellitus

(Intern Med 60: 829-837, 2021)

DOI: 10.2169/internalmedicine.5930-20)
Patients with chronic liver disease (CLD) often have thrombocytopenia. In liver cirrhosis, 76% of patients manifest this complication (1, 2). Patients with CLD require invasive procedures frequently, including liver biopsies, radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) and endoscopic variceal ligation (EVL) and endoscopic injection sclerotherapy (EIS) for esophageal varices. Severe thrombocytopenia (platelet count <5.0×10⁴/μL) can significantly increase the risk of hemorrhagic events during invasive procedures (1).

In patients with thrombocytopenia scheduled to undergo invasive procedures, prophylactic platelet transfusions are often performed to prevent hemorrhagic events during and after the procedure; however, no consensus has been reached on the appropriate threshold platelet level for initiating prophylactic treatment in patients with CLD (1, 3, 4). Prophylactic transfusions must be repeated within 3-4 days as needed because transfused platelets have a short lifespan (4). Platelet transfusion has several complications and limitations, including febrile nonhemolytic and allergic reactions, infection risk, refractoriness to transfusion due to human leucocyte antigen alloimmunization, need for hospitalization, and cost (3-6). Platelet transfusions should thus be used on a minimal basis and carefully administered.

Lusutrombopag, an oral thrombopoietin (TPO) receptor agonist, was developed to reduce the need for patients with CLD to receive prophylactic platelet transfusions prior to invasive procedures (7, 8). Lusutrombopag induces platelet production by acting on the transmembrane domain of the human TPO receptor and activating the signaling pathway in the same way as endogenous TPO (7).

Lusutrombopag treatment efficiently increases platelet counts and makes it possible for patients with CLD and thrombocytopenia to receive invasive procedures (8-12). In this study, we assessed the efficacy of repeated lusutrombopag treatment and the factors associated with a response to lusutrombopag.

### Materials and Methods

#### Patients

A total of 39 patients with CLD who were judged by attending physicians to need treatment for thrombocytopenia prior to their invasive procedure received lusutrombopag treatment at our hospital and affiliated hospitals between December 2015 to December 2018. These 39 patients were enrolled in the present retrospective study.

Table 1 lists the baseline characteristics of patients enrolled in this study. Of the 39 patients, 29 received the lusutrombopag therapeutic regimen only once, and 10 received lusutrombopag more than once (2 treatment regimens, n=7; 3 regimens, n=2; 4 regimens, n=1). The scheduled invasive procedures were as follows: EIS or EVL (16 patients, 30%)

### Table 1. Baseline Characteristics of 39 Patients who Received Lusutrombopag Treatment.

| Characteristic                              | Value |
|--------------------------------------------|-------|
| Age (years)                                | 70 (38-94) |
| Gender (male/female)                       | 24/15 |
| Body mass index (kg/m²)                    | 24.9 (15.2-35.7) |
| Type of hepatitis [CHC (SVR)/CHB/ALD/NASH/AIH] | 14[10]/5/9/9/2 |
| Child-Pugh class (A/B)                     | 20/19 |
| Ascites (none/mild/moderate to severe)     | 28/7/4 |
| Hepatic encephalopathy (none/Grade I-II/ Grade III-IV) | 38/1/0 |
| Gastroesophageal varices (+/-)             | 14/25 |
| Spleen index (cm²)                         | 68.1 (26.7-133.2) |
| Liver cancer (+/-)                         | 24/15 |
| Diabetes mellitus (+/-)                    | 20/19 |
| Hypertension (+/-)                         | 24/15 |
| Baseline platelet count (×10⁴/μL)          | 4.6 (1.3-8.6) |
| White blood cell (μL)                      | 3,500 (1,890-6,500) |
| Hemoglobin (g/dL)                          | 12.1 (7.7-15.7) |
| Prothrombin time (%)                       | 75 (47.0-100.8) |
| Total bilirubin (mg/dL)                    | 1.57 (0.4-7.2) |
| Aspartate aminotransferase (U/L)           | 35 (14-111) |
| Alanine aminotransferase (U/L)             | 25.0 (6-82) |
| Albumin (g/dL)                             | 3.5 (2.8-4.6) |
| Creatinine (g/dL)                          | 0.80 (0.43-2.71) |

Categorical data are represented as numbers of patients, and continuous data are represented as medians and range. CHC: chronic hepatitis C, SVR: sustained viral response, CHB: chronic hepatitis B, ALD: alcoholic liver disease, NASH: nonalcoholic steatohepatitis, AIH: autoimmune hepatitis
TACE (12 patients, 23%), a liver biopsy (6 patients, 11%), minor procedure (6 patients, 11%), tooth extraction (5 patients, 9%), thoracentesis or abdominal paracentesis (3 patients, 6%), RFA (2 patients, 4%), endoscopic mucosal resection or endoscopic submucosal dissection (2 patients, 4%) and a percutaneous needle biopsy of the thyroid gland (1 patient, 2%). Pretreatment plasma concentrations of thrombopoietin were measured in 14 patients by a chemiluminescent enzyme.

The attending physicians diagnosed diabetes mellitus (type 2) according to the guidelines of the Japanese Diabetes Society (13). The median blood glucose level and hemoglobin A1c of 19 patients with diabetes mellitus was 130 mg/dL (range, 86-273 mg/dL) and 6.5% (range, 5.1-8.3%), respectively. As the treatment for patients with diabetes mellitus, seven different medicines were used, including insulin preparation, dipeptidyl peptidase-4 inhibitor, α-glucosidase inhibitor, sulfonlurea, glinide, biguanide and glucagon like peptide-1 receptor agonist. Two patients received monotherapy, five were given two drugs, six received three drugs, and two received four different drugs. Four patients were not treated with medicinal therapy. Seven (37%) of the 19 patients with diabetes mellitus were poorly controlled (hemoglobin A1c ≥7.0%). The spleen index was calculated by multiplying the major diameter by the minor diameter measured by abdominal ultrasonography before the lusutrombopag treatment (14).

This study was approved by each hospital’s ethics committee and confirmed to comply with the Declaration of Helsinki prior to data collection.

**Lusutrombopag treatment**

On day 1, patients started receiving 3 mg lusutrombopag per os (p.o). Lusutrombopag treatment was basically continued for 7 days. If the platelet count had reached 5.0×10⁴/μL and increased more than 2.0×10⁴/μL from baseline, the administration of lusutrombopag was stopped on days 5, 6, or 7 to prevent an excessive increase in the platelet count. The invasive procedure of each patient was performed between days 7 and 18 after the initiation of lusutrombopag. Patients did not receive other TPOs during this period.

**Assessments of the response to therapy and safety**

Changes in platelet counts were evaluated for up to five weeks after lusutrombopag treatment. Three patients received a platelet transfusion. In these three patients, the only platelet counts that were obtained were those before the administration of a platelet transfusion. A “responder” to lusutrombopag treatment was defined as a patient whose platelet count increased more than 2.0×10⁴/μL from baseline before the invasive procedure; all others were considered “non-responders.” The safety of lusutrombopag treatment was evaluated based on adverse drug reactions and the results of clinical laboratory testing, a physical examination, vital signs and ultrasonography or computed tomography. Clinical laboratory testing was performed prior to administration, before invasive procedures, one week after invasive procedures and four weeks after invasive procedures.

**Statistical analyses**

Categorical variables were expressed as frequencies, while continuous variables were expressed as medians with ranges. A univariate analysis was used to investigate the relationship between the various clinical variables in the responder and the non-responder patients at the first administration of lusutrombopag. The Mann-Whitney U test and Fisher’s exact test were used as appropriate to examine the statistical significance of differences between groups. To identify predictive factors for the efficacy of lusutrombopag treatment during the first administration of the agent, a logistic regression analysis was used. For all analyses, a p value <0.05 was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (15).

**Results**

**Changes in platelet counts due to lusutrombopag treatment and safety**

A total of 39 patients received the lusutrombopag protocol for 53 invasive procedures. Of the 53 procedures, 50 were preceded by lusutrombopag administration for 7 days, and 3 were preceded by lusutrombopag administration for 5 days due to meeting the criteria for the early cessation of treatment. The median platelet count significantly increased from 4.5×10⁴/μL before lusutrombopag treatment to 7.2×10⁴/μL before the invasive procedure, and to 8.9×10⁴/μL at 1 week after the invasive procedure (Fig. 1). In 35 out of 53 (66%) procedures, the patients undergoing the procedure satisfied the response criterion. Of the 18 procedures in which the patient did not satisfy the response criterion, 1 invasive procedure was canceled, 3 patients underwent the invasive procedure following platelet transfusion, and 14 invasive procedures were performed without platelet transfusion. Lusutrombopag treatment ultimately allowed patients to undergo 49 of 53 (92%) invasive procedures without platelet transfusion.

No bleeding complications occurred either during or after any of the 49 invasive procedures performed without platelet transfusion. No patients developed portal thrombus following lusutrombopag treatment as analyzed by ultrasonography or computed tomography, and no other significant adverse events were observed.

**Effect of repeated lusutrombopag treatment**

In this study, 10 patients underwent invasive procedures 2 or more times and received lusutrombopag treatment more than once. Table 2 summarizes the baseline characteristics of the 10 patients who received lusutrombopag treatment repeatedly. The median interval between the first and second administration was 95 days (range, 36-742 days). The me-
Figure 1. Changes in platelet counts in patients undergoing lusutrombopag treatment. In these box-and-whisker plots, the lines within the boxes represent the median values; the upper and lower lines of the boxes represent the 75th and 25th percentiles, respectively. N.S.: not significant

Table 2. Baseline Characteristics of 10 Patients who Received Repeat- ed Lusutrombopag Treatment.

| Characteristic                              | Value                  |
|--------------------------------------------|------------------------|
| Age (years)                                | 69 (52-79)             |
| Gender (male/female)                       | 7/3                    |
| Body mass index (kg/m²)                    | 25.0 (20.6-33.2)       |
| Type of hepatitis [CHC (SVR)/CHB/ALD/NASH/AIH] | 4[3]/1/1/1             |
| Child-Pugh class (A/B)                     | 3/7                    |
| Ascites (none/mild/moderate to severe)     | 6/3/1                  |
| Hepatic encephalopathy (none/Grade I-II/ Grade III-IV) | 10/0/0                |
| Gastroesophageal varices (-/+              | 1/9                    |
| Spleen index (cm²)                         | 79.5 (42.6-126.4)      |
| Liver cancer (-/+                          | 6/4                    |
| Diabetes mellitus (-/+                     | 5/5                    |
| Hypertension (-/+                          | 6/4                    |
| Baseline platelet count (×10⁴/μL)          | 3.3 (1.9-8.4)          |
| White blood cell (μL)                      | 2,850 (1,900-4,200)    |
| Hemoglobin (g/DL)                          | 12.4 (9.6-15.6)        |
| Prothrombin time (%)                       | 67.5 (55.3-97.7)       |
| Total bilirubin (mg/dL)                    | 1.65 (0.6-3.3)         |
| Aspartate aminotransferase (U/L)           | 29.5 (21-86)           |
| Alanine aminotransferase (U/L)             | 18.5 (10-69)           |
| Albumin (g/dL)                             | 3.3 (2.9-5.0)          |
| Creatinine (g/dL)                          | 0.87 (0.40-2.16)       |

Categorical data are represented as numbers of patients, and continuous data are represented as medians and range. CHC: chronic hepatitis C, SVR: sustained viral response, CHB: chronic hepatitis B, ALD: alcoholic liver disease, NASH: nonalcoholic steatohepatitis, AIH: autoimmune hepatitis.
count before the second administration of lusutrombopag was $3.3 \times 10^4 / \mu L$ and significantly increased to $6.7 \times 10^4 / \mu L$ before the invasive procedure and to $8.6 \times 10^4 / \mu L$ at 1 week after the invasive procedure (Fig. 2). The effects of lusutrombopag were not significantly different between the first and second administration.

Factors associated with the response to lusutrombopag treatment

Twenty-five of 39 (64%) patients satisfied the criterion of responder to the first administration of lusutrombopag. We analyzed factors associated with response to lusutrombopag treatment. According to a univariate analysis, the spleen index and diabetes mellitus were significantly associated with the response to lusutrombopag treatment. A multivariate analysis identified the absence of diabetes mellitus (odds ratio, 5.56 for presence; p=0.04) as a significant and independent predictor for a response to lusutrombopag treatment (Table 3).

Effect of lusutrombopag in patients with diabetes mellitus

The relationship between diabetes mellitus (type 2) and the effect of lusutrombopag was assessed. The median platelet counts before lusutrombopag treatment were not significantly different between patients with and without diabetes mellitus ($5.1 \times 10^4 / \mu L$ and $4.5 \times 10^4 / \mu L$, respectively) (Fig. 3). After lusutrombopag treatment, the median platelet count was significantly higher in patients without diabetes mellitus than in those with diabetes mellitus before ($9.0 \times 10^4 / \mu L$ and $5.2 \times 10^4 / \mu L$, respectively) and 1 week after the invasive procedure ($10.5 \times 10^4 / \mu L$ and $6.6 \times 10^4 / \mu L$, respectively). Lusutrombopag was less effective for patients with diabetes mellitus than for those without it.

We hypothesized that the baseline TPO level was related to the effect of lusutrombopag and measured plasma the TPO levels in 14 lusutrombopag-treated patients with or without diabetes mellitus. The mean baseline TPO level was higher in patients with diabetes mellitus than in those without diabetes mellitus (0.62 and 0.49 fmol/mL, respectively) but was not significantly different between these groups (Fig. 4).

Discussion

Patients with thrombocytopenia due to CLD often repeatedly required invasive procedures, such as RFA, TACE, EVL, and EIS. Information on the efficacy of repeated use of lusutrombopag is scarce (9-12). Furthermore, although severe thrombocytopenia and an increased splenic volume have been reported to impede the ability of lusutrombopag to improve platelet counts sufficiently (16-18), the factors associated with the treatment response to lusutrombopag are unclear. In this study, the efficacy and safety of repeated lusutrombopag treatment were determined. Patients with diabetes mellitus might show a decreased response to lusutrombopag treatment.

In our study, lusutrombopag treatment significantly increased the platelet count in patients undergoing 35 of 53 (66%) procedures and enabled patients to undergo 49 of 53...
Table 3. Factors Associated with Response to Lusutrombopag Treatment.

| Characteristic                                         | Responder (n=25) | Non-responder (n=14) | Univariate analysis p value | Multivariate analysis Odds ratio (95% CI) p value |
|--------------------------------------------------------|------------------|----------------------|----------------------------|-----------------------------------------------|
| Age (years)                                            | 67 (38-94)       | 71 (43-81)           | 0.93                       |                                               |
| Gender (male/female)                                   | 13/12            | 11/3                 | 0.171                      |                                               |
| Body mass index (kg/m²)                                | 24.5 (17.1-31.5) | 25.6 (15.2-35.7)     | 0.672                      |                                               |
| Child-Pugh class (A/B)                                 | 13/12            | 7/7                  | 1.00                       |                                               |
| Ascites (none/mild/moderate to severe)                 | 18/4/3           | 10/3/1               | 1.00                       |                                               |
| Hepatic encephalopathy (none/Grade I/II/Grade III-IV)  | 24/1/0           | 14/0/0               | 1.00                       |                                               |
| Gastroesophageal varices (+/-)                         | 10/15            | 4/10                 | 0.729                      |                                               |
| Spleen index (cm²)                                     | 55.4 (26.7-101.9)| 81.8 (32.7-133.2)    | 0.0256                     |                                               |
| Liver cancer (+/-)                                     | 15/10            | 9/5                  | 1.00                       |                                               |
| Diabetes mellitus (-/+                                  | 16/9             | 4/10                 | 0.0484                     | 5.56 (1.05-29.3) 0.04                       |
| Hypertension (+/-)                                     | 18/7             | 6/8                  | 0.0953                     |                                               |
| Baseline platelet count (×10⁹/µL)                      | 5.1 (2.5-8.6)    | 4.1 (1.3-8.5)        | 0.155                      |                                               |
| White blood cell (/µL)                                 | 3,500 (1,890-6,500) | 3,535 (2,130-4,300) | 0.682                      |                                               |
| Hemoglobin (g/dL)                                      | 13.0 (7.7-15.7)  | 11.45 (9.0-15.4)     | 0.356                      |                                               |
| Prothrombin time (%)                                   | 78.1 (51-100.8)  | 71.9 (47-87.8)       | 0.0551                     |                                               |
| Total bilirubin (mg/dL)                                | 1.8 (0.4-3.8)    | 1.1 (0.4-7.2)        | 0.0892                     |                                               |
| Aspartate aminotransferase (U/L)                       | 31 (14-111)      | 38 (21-67)           | 0.086                      |                                               |
| Alanine aminotransferase (U/L)                         | 24 (6-82)        | 28 (15-55)           | 0.164                      |                                               |
| Albumin (g/dL)                                         | 3.5 (2.9-4.5)    | 3.45 (2.8-4.6)       | 0.639                      |                                               |
| Creatinine (g/dL)                                      | 0.76 (0.43-2.71) | 0.845 (0.45-1.10)    | 0.272                      |                                               |

Categorical data are represented as numbers of patients, and continuous data are represented as medians and range. CI: confidence interval.

Figure 3. Changes in platelet counts in patients with and without diabetes mellitus. In these box-and-whisker plots, the lines within the boxes represent the median values; the upper and lower lines of the boxes represent the 75th and 25th percentiles, respectively. N.S.: not significant.

(92%) invasive procedures without platelet transfusion. All patients completed the procedures without bleeding complications. Regarding safety, 1.9% of the patients who were given lusutrombopag developed thrombotic events, a frequency that was similar to that in the placebo group in a global phase 3 trial (19). In the present study, no patients developed portal thrombus following lusutrombopag treatment as analyzed by ultrasonography or computed tomography, and no other significant adverse events were observed.

The present study included some patients with baseline
platelet counts ≥5.0x10⁴/μL who were advised by attending physicians to receive thrombocytopenia treatment before undergoing invasive procedures. There are currently no globally accepted clinical guidelines for administering platelet transfusions for patients with CLD who undergo invasive procedures (20). The cut-off value for the administration of prophylactic platelet transfusions varies depending on the patient’s clinical condition and planned invasive procedure (1). Although clinical trials have been performed for patients with baseline platelet counts <5.0x10⁴/μL, it was recently reported that lusutrombopag treatment in patients with platelet counts ≥5.0x10⁴/μL was effective without any adverse reactions (21). In fact, that study also found a significant increase in platelet counts and no significant adverse event in patients with baseline platelet counts ≥5.0x10⁴/μL. In patients with platelet count ≥5.0x10⁴/μL, a further analysis will be needed to clarify the need for and safety of lusutrombopag.

Patients with CLD often require repeated invasive procedures because esophageal varices or HCC are likely to relapse in such patients, especially in patients with liver cirrhosis. In the present study, 10 patients received lusutrombopag treatment more than once. The platelet counts significantly increased following the second administration of lusutrombopag, and the effects of lusutrombopag were not significantly different between the first and second administrations, findings similar to those in previous reports (9-12). This result indicates that lusutrombopag treatment produces identical effects even after repeated use. For patients needing repeated invasive procedures, lusutrombopag treatment appears to be more useful than repeated platelet transfusions.

Severe thrombocytopenia, spleen size and hemoglobin levels have been reported as predictors associated with the effects of lusutrombopag in Japan. Hirooka et al. reported that baseline platelet counts <3.0x10⁴/μL were significantly associated with non-achievement of maximum platelet counts >5.0x10⁴/μL after the administration of lusutrombopag (17). Uojima et al. showed that an increased spleen volume was negatively related to an increased platelet count after lusutrombopag treatment, and the cut-off value of the spleen volume was 855 mL (18). Furuichi et al. pointed out that the hemoglobin level and spleen index were negatively correlated with an increase in platelet counts (22). In the present study, a multivariate analysis identified the absence of diabetes mellitus as a significant independent predictor for a response to lusutrombopag treatment.

Diabetes mellitus is known to be associated with significant changes in blood platelets, including an increased mean platelet volume and numbers of reticulated platelets (23, 24). TPO stimulates the proliferation of megakaryocytes and increases the production of platelets (24, 25). Serum TPO levels in patients with liver cirrhosis and thrombocytopenia are lower than in healthy persons (26), and the progressive decline in the liver function of patients with hepatitis C virus-related CLD is associated with a decrease in TPO production (27). Kraakman et al. showed that high blood glucose levels trigger neutrophils to release S100 calcium-binding protein A8/A9, which interacts with receptors for advanced glycation end-products on Kupffer cells (25). The interaction leads to increased interleukin-6 production and ultimately results in increased TPO production in the liver (25). We therefore hypothesized that the efficacy of lusutrombopag...
might be limited for patients with diabetes mellitus because of elevated baseline TPO levels. The mean baseline TPO level was not significantly different but was higher in patients with diabetes mellitus than in those without diabetes mellitus. Patients with diabetes mellitus may have a low susceptibility to lusutrombopag due to high baseline TPO levels. Further analyses will be required to determine the reason for the low efficacy of lusutrombopag in patients with diabetes mellitus.

In cirrhotic patients, partial splenic embolization and splenectomy are also effective against thrombocytopenia (4, 28). These procedures have been used for patients with not only CLD but also idiopathic thrombocytopenic purpura (29). However, these procedures are frequently associated with adverse events, such as a fever, the development of portal thrombosis and the occurrence of liver abscess. Although the effect of lusutrombopag is transient, this treatment seems to be safer for CLD patients than splenectomy or partial splenic embolization.

One limitation of the present study is the small number of patients, especially patients with diabetes mellitus. No significant difference in baseline thrombopoietin concentrations was observed between patients with and without diabetes mellitus, which may be due to the small number of diabetic patients. Therefore, a further analysis with a larger number of patients will be needed to clarify the factors associated with response to lusutrombopag and the relationship between the effect of lusutrombopag and diabetes mellitus.

In conclusion, lusutrombopag treatment significantly increased platelet counts in CLD patients and allowed them to undergo invasive procedures. The treatment produced identical effects when it was used repeatedly. Patients with diabetes mellitus might show a decreased response to lusutrombopag treatment.

Author’s disclosure of potential Conflicts of Interest (COI).
Michio Imamura: Research funding, Bristol-Myers Squibb and AbbVie. Kazuaki Chayama: Honoraria, Bristol-Myers Squibb, MSD, AbbVie, Gilead Science, Dainippon Sumitomo Pharma and Mitsubishi Tanabe Pharma; Research funding, Gilead Science, Dainippon Sumitomo Pharma, MSD, AbbVie, Eisai, TORYAY, Otsuka Pharma, Chugai Pharma, Takeda Pharma and Rosche.

Financial Support
The study was supported in part by research funding from the Research Program on Hepatitis from the Japan Agency for Medical Research and Development, AMED (grant number: 19fk0210020h0003).

Acknowledgement
We thank Akemi Sata and Emi Nishio for their technical assistance.

References
1. Afidhal N, McHutchison J, Brown R, et al. Thrombocytopenia associated with chronic liver disease. J Hepatol 48: 1000-1007, 2008.
2. Giannini EG. Review article: thrombocytopenia in chronic liver disease and pharmacologic treatment options. Aliment Pharmacol Ther 23: 1055-1065, 2006.
3. Tateishi R, Seike M, Kudo M, et al. A randomized controlled trial of lusutrombopag in Japanese patients with chronic liver disease undergoing radiofrequency ablation. J Gastroenterol 54: 171-181, 2019.
4. Hayashi H, Beppu T, Shirabe K, Maehara Y, Baba H. Management of thrombocytopenia due to liver cirrhosis: a review. World J Gastroenterol 20: 2595-2605, 2014.
5. McCullough J. Current issues with platelet transfusion in patients with cancer. Semin Hematol 37 (2 Suppl 4): 3-10, 2000.
6. Perrotta PL, Snyder EL. Non-infectious complications of transfusion therapy. Blood Rev 15: 69-83, 2001.
7. Kim ES. Lusutrombopag: first global approval. Drugs 76: 155-158, 2016.
8. Hidaka H, Kurosaki M, Tanaka H, et al. Lusutrombopag reduces need for platelet transfusion in patients with thrombocytopenia undergoing invasive procedures. Clin Gastroenterol Hepatol 17: 1192-1200, 2019.
9. Sato S, Miyake T, Kataoka M, et al. Efficacy of repeated lusutrombopag administration for thrombocytopenia in a patient scheduled for invasive hepaticcellular carcinoma treatment. Intern Med 56: 2887-2890, 2017.
10. Ishikawa T, Okoshi M, Tomiyoshi K, et al. Efficacy and safety of repeated use of lusutrombopag prior to radiofrequency ablation in patients with recurrent hepaticcellular carcinoma and thrombocytopenia. Hepatol Res 49: 590-593, 2019.
11. Kawaratahi H, Tsuji Y, Ishida K, et al. The effect of three or more administrations of lusutrombopag in patients with cirrhotic thrombocytopenia: a retrospective single-center study. Hepatol Res. Forthcoming.
12. Sasaki R, Shiino C, Imawari M, et al. Safety and effectiveness of lusutrombopag in Japanese chronic liver disease patients with thrombocytopenia undergoing invasive procedures: interim results of a postmarketing surveillance. Hepatol Res 49: 1169-1181, 2019.
13. Kuzuya T, Nakagawa S, Satoh J, et al. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. Diabetes Res Clin Pract 55: 65-85, 2002.
14. Koga T, Morikawa Y. Ultrasonographic determination of the splenic size and its clinical usefulness in various liver diseases. Radiology 115: 157-161, 1975.
15. Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant 48: 452-458, 2013.
16. Takada H, Kurosaki M, Nakanishi H, et al. Real-life experience of lusutrombopag for cirrhotic patients with low platelet counts being prepared for invasive procedures. PLoS One 14: e0211122, 2019.
17. Hirooka M, Ochi H, Hiraoka A, et al. Role of severe thrombocytopenia in preventing platelet count recovery in thrombocytopenic patients with chronic liver disease. J Gastroenterol Hepatol 35: 299-304, 2020.
18. Uojima H, Arase Y, Itohka N, et al. Relationship between response to lusutrombopag and splenic volume. World J Gastroenterol 24: 5271-5279, 2018.
19. Peck-Radosavljevic M, Simon K, Iacobellis A, et al. Lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease undergoing invasive procedures (L-PLUS 2). Hepatology 70: 1336-1348, 2019.
20. Maan R, de Knegt RJ, Veldt BJ. Management of thrombocytopenia in chronic liver disease: focus on pharmacotherapeutic strategies. Drugs 75: 1981-1992, 2015.
21. Tsuji Y, Kawaratanii H, Ishida K, et al. Effectiveness of lusutrombopag in patients with mild to moderate thrombocytopenia. Dig
Furuichi Y, Takeuchi H, Yoshimasu Y, Kasai Y, Abe M, Itoi T. Thrombopoietin receptor agonist is more effective than platelet transfusion for chronic liver disease with thrombocytopenia, shown by propensity score matching. Hepatol Res. Forthcoming.

Tschoepe D, Roesen P, Esser J, et al. Large platelets circulate in an activated state in diabetes mellitus. Semin Thromb Hemost 17: 433-438, 1991.

Lee RH, Bergmeier W. Sugar makes neutrophils RAGE: linking diabetes-associated hyperglycemia to thrombocytosis and platelet reactivity. J Clin Invest 127: 2040-2043, 2017.

Kraakman MJ, Lee MK, Al-Sharea A, et al. Neutrophil-derived S100 calcium-binding proteins A8/A9 promote reticulated thrombocytosis and atherogenesis in diabetes. J Clin Invest 127: 2133-2147, 2017.

Rios R, Sangro B, Herrero I, Quiroga J, Prieto J. The role of thrombopoietin in the thrombocytopenia of patients with liver cirrhosis. Am J Gastroenterol 100: 1311-1316, 2005.

Giannini E, Botta F, Borro P, et al. Relationship between thrombopoietin serum levels and liver function in patients with chronic liver disease related to hepatitis C virus infection. Am J Gastroenterol 98: 2516-2520, 2003.

Ishikawa T, Abe S, Kojima Y, et al. Telaprevir-based triple therapy following partial splenic arterial embolization for chronic hepatitis C with thrombocytopenia can reduce carcinogenesis and improve hepatic function reserve. Exp Ther Med 10: 1334-1338, 2015.

Rijcken E, Mees ST, Bisping G, et al. Laparoscopic splenectomy for medically refractory immune thrombocytopenia (ITP): a retrospective cohort study on longtime response predicting factors based on consensus criteria. Int J Surg 12: 1428-1433, 2014.