Lusutrombopag is Effective and Safe in Patients with Chronic Liver Disease and Severe Thrombocytopenia: A Multicenter Retrospective Study

Hiroaki Nomoto  
Jichi Ika Daigaku

Naoki Morimoto  
Jichi Ika Daigaku

Kouichi Miura (miura385@jichi.ac.jp)  
Jichi Ika Daigaku

Shunji Watanabe  
Jichi Ika Daigaku

Yoshinari Takaoka  
Jichi Ika Daigaku

Hiroshi Maeda  
Jichi Ika Daigaku

Takahiro Sasaki  
Jichi Ika Daigaku

Yohei Koyashiki  
Jichi Ika Daigaku

Hidekazu Kurata  
Tochigi Medical Center Shimotsuga

Norikatsu Numao  
Haga Red Cress Hospital

Norio Isoda  
Jichi Ika Daigaku

Hironori Yamamoto  
Jichi Ika Daigaku

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Abstract

**Background:** Chronic liver disease (CLD) is often complicated by severe thrombocytopenia (platelet count <50,000/µL). Platelet transfusion has been a gold standard for increasing the platelet count to prevent hemorrhagic events in such patients. Lusutrombopag, a thrombopoietin receptor agonist, can increase the platelet count in such patients when invasive procedures are scheduled. However, we have little information on the effect of lusutrombopag in CLD patients with severe thrombocytopenia in real-world settings.

**Methods:** To investigate the efficacy and safety of lusutrombopag in patients with chronic liver disease and severe thrombocytopenia, we retrospectively investigated 26 CLD patients with a platelet count of <50,000/µL. Lusutrombopag, 3 mg once daily, was administered 8-15 days before scheduled invasive procedures.

**Results:** Among 26 patients who received lusutrombopag, 19 patients (73.1%) patients showed a platelet count of ≥50,000/µL (Group A) and did not require platelet transfusion. The remaining 7 patients (26.9%) did not reach platelet ≥50,000/µL (Group B). The means of platelet increase were 36,000/µL and 13,000/µL in groups A and B, respectively. A low platelet count at baseline was a characteristic of patients in group B. Among 13 patients who repeatedly used lusutrombopag, lusutrombopag significantly increased the platelet count as the initial treatment. No adverse events were noted during or after lusutrombopag treatment. In addition, the degree of platelet increase with lusutrombopag was larger than that in their previous platelet transfusion.

**Conclusions:** Lusutrombopag is effective and safe for CLD patients with a platelet count of <50,000/µL.

Background

Chronic liver disease (CLD) is frequently complicated by thrombocytopenia (1). Indeed, 10% of patients with cirrhosis show platelet counts of < 50,000/µL (2), a criterion for platelet transfusion when invasive procedures are required (3). In fact, these patients often have hepatocellular carcinoma and gastrointestinal varices, which require invasive therapeutic procedures, including radiofrequency ablation and ligation/sclerotherapy, respectively. These invasive procedures is associated with an increased risk of bleeding events (4). Thus, it is necessary to increase the platelet count to prevent hemorrhagic events.

Platelet transfusion has been a gold standard to increase platelet count. However, platelet transfusion is associated with several problems, including the risk of unknown infection, allergic reaction and a shortage of donors (5). In addition, repeated platelet transfusion may induce refractoriness to subsequent platelet transfusion. Furthermore, the efficacy of platelet transfusion is likely to be limited (1). Thus, alternative methods to platelet transfusion are required to resolve such problems.

In the USA, FDA approved two thrombopoietin receptor agonists, avatrombopag and lusutrombopag, in 2018(6). These thrombopoietin receptor agonists showed favorable results to increase platelet count in
clinical trials (7)(8)(9). In Japan, lusutrombopag was approved for CLD patients with thrombocytopenia in 2015(10). Japanese real-world data demonstrated that 84–96% of patients who received lusutrombopag treatment did not require platelet transfusion before their scheduled invasive procedure (11)(12)(13). In addition, the increase in the platelet count achieved by lusutrombopag was superior to that did by platelet transfusion (14). Furthermore, in patients who received lusutrombopag repeatedly, the increase in the platelet count was similar to that in the initial treatment (15)(16). Adverse events related to lusutrombopag were limited. Thus, lusutrombopag is now one of the choices of treatment for increasing the platelet count in CLD patients with thrombocytopenia.

Although lusutrombopag showed favorable effects in CLD patients with thrombocytopenia, the real-world data on lusutrombopag included patients with a platelet count of > 50,000/µL at baseline (11)(12)(13); thus, some of these patients would not have required platelet transfusion (3). We therefore investigated the efficacy and safety of lusutrombopag in the real-world among patients with platelet counts of < 50,000/µL, which is generally accepted as a criterion for platelet transfusion.

**Methods**

**Patients**

We performed a multicenter retrospective study from April 2016 to April 2020. CLD patients with severe thrombocytopenia (< 50,000/µL) were enrolled in the present study. The leading exclusion criteria were portal vein thrombosis, lusutrombopag allergy, splenectomy, partial splenic embolization before lusutrombopag treatment and Child-Pugh class C. Lusutrombopag (3 mg once daily [Mulpleta, Shionogi & Co., Ltd., Osaka, Japan]) was started 8–15 days before a scheduled invasive procedure. On day 5, lusutrombopag was discontinued if the platelet count was ≥ 50,000/µL with an increase of ≥ 20,000/µL. Lusutrombopag was continued 2 more days when platelet count did not reach 50,000/µL. After the administration of lusutrombopag for 5 or 7 days, the platelet count was monitored every 2–4 days until after the procedure. When the platelet count was < 50,000/µL before the procedure, 10 units of platelets (> 2 × 10^{11}) were transfused. Portal vein thrombosis was monitored by abdominal ultrasonography and/or computed tomography (CT). The Albumin-Bilirubin (ALBI) grade and fibrosis-4 (FIB4) index were calculated according to published formulas (17)(18). The splenic volume was measured on CT examinations. We divided the patients into two groups according to the response to lusutrombopag: group A included patients with a platelet counts of ≥ 50,000/ µL after lusutrombopag treatment; group B included patients with a platelet count of < 50,000/ µL. Thus, the patients in group A did not require platelet transfusion before the invasive treatment. In addition to lusutrombopag treatment, we investigated the efficacy of platelet transfusion. Ten units of platelets (≥ 2 × 10^{11}) were transfused just before the invasive procedure when the platelet count was < 50,000/µL. The platelet count was determined on the next day after the procedure in cases of platelet transfusion.

**Statistical analyses**
The results were analyzed by the chi-squared test, Wilcoxon signed rank test, and univariate and multivariate logistic regression analyses. All statistical analyses were performed using the Stata15 software program (STATA Corporation, College Station, TX, USA). p values of < 0.05 were considered to indicate statistical significance.

Results

The efficacy of lusutrombopag

Table 1 shows the characteristics of all 26 patients at the first administration of lusutrombopag. There were 19 (73.1%) and 7 (26.9%) patients in groups A and B, respectively. Group B was characterized by a male predominance, low platelet count at baseline and a high splenic volume. However, there were no significant differences in age, Child-Pugh score, ALBI score, FIB4 index or Mac-2 binding protein glycosylation isomer between groups A and B.
Table 1
The characteristics of patients who received lusutrombopag

|                                | All | Group A | Group B | p-value |
|--------------------------------|-----|---------|---------|---------|
| n                              | 26  | 19      | 7       |         |
| Male/Female                    | 18/8| 11/8    | 7/0     | 0.0357  |
| Age (years)                    | 65.8 ± 7.5 | 66.4 ± 7.5 | 64.3 ± 7.3 | 0.5817  |
| Lusutrombopag 5/7days          | 2/24| 2/17    | 0/7     | 0.3706  |
| History of platelet transfusion| 13/26(50%) | 8/19(42%) | 5/7(71%) | 0.1847  |
| HCV/HBV/NASH/ALC/Others        | 13/2/3/5/3 | 9/2/2/3/3 | 4/0/1/2/0 |         |
| Child-Pugh A/B                 | 13/13| 9/10    | 4/3     | 0.6583  |
| Child-Pugh score               | 6.85 ± 1.35 | 6.84 ± 1.31 | 6.86 ± 1.46 | 0.9525  |
| ALBI                           | -2.03 ± 0.63 | -1.91 ± 0.60 | -2.36 ± 0.57 | 0.1118  |
| FIB-4                          | 13.85 ± 4.49 | 13.97 ± 4.94 | 13.53 ± 2.94 | 0.8851  |
| M2BPGi (COI)                   | 9.99 ± 5.18  | 10.35 ± 5.47 | 8.57 ± 3.44 | 0.4497  |
| TACE/RFA/EVL/Others            | 10/7/5/4 | 7/6/3/3 | 3/1/2/1 |         |
| Platelet count                 |     |         |         |         |
| <3.5/3.5–4.5/4.5<              | 8/12/6 | 3/10/6 | 5/2/0 |         |
| Baseline (x10⁴/uL)             | 3.9 ± 0.77 | 4.2 ± 0.56 | 3.0 ± 0.59 | 0.0012  |
| Splenic volume (mL)            | 684 ± 337 | 582 ± 278 | 960 ± 327 | 0.0152  |

HCV: hepatitis C virus; HBV: hepatitis B virus; NASH: non-alcoholic steatohepatitis; ALC: alcohol; ALBI: albumin-bilirubin; FIB-4: fibrosis-4; M2BPGi: mac2 binding protein glucosylation isomer; TACE: transcatheter arterial chemoembolization; RFA: radiofrequency ablation; EVL: endoscopic variceal ligation

Lusutrombopag significantly increased the platelet count in all 26 patients with a mean increase of 30,000/µL (Fig. 1a, left panel). The degree of increase in the platelet count in group A was larger than that in group B (Fig. 1a, middle and right panels). In group A, 94.7% (18/19) of the patients showed a platelet increase of ≥ 20,000/ µL. In contrast, only 28.6% (2/7) of the patients in group B showed a platelet increase of ≥ 20,000/ µL. The days required to reach the maximum platelet counts did not differ between groups A and B. Among 7 patients in group B, 6 received platelet transfusions due to a low platelet count of < 50,000/µL, even after lusutrombopag treatment (one patient failed to receive a platelet transfusion). However, the increase in the platelet count after platelet transfusion was not statistically significant (Fig. 1b).
Factors that interfered with the achievement of a platelet count of $\geq 50,000$ on lusutrombopag treatment.

We identified factors that interfered with the achievement of a platelet count of $\geq 50,000/\mu L$ after the initiation of lusutrombopag. In accordance with previous reports, a low platelet count at baseline (19) and a high splenic volume (11)(12) were identified as associated factors in a univariate analysis. A multivariate analysis demonstrated that a low platelet count at baseline was significantly associated with failure to achieve a platelet count of $\geq 50,000/\mu L$ (Table 2). Indeed, all patients with a platelet count of $<30,000/\mu L$ failed to achieve a platelet count of $\geq 50,000/\mu L$ after lusutrombopag treatment. Although we tried to identify the factors that contribute to increase of platelet count $\geq 20,000/\mu L$ from the baseline, no such factors, including platelet count at baseline and splenic volume, were identified in the univariate or multivariate analyses (data not shown).

|                      | Univariate analysis | Multivariate analysis |
|----------------------|---------------------|-----------------------|
|                      | OR (95% CI)         | p-value               | OR (95% CI)         | p-value   |
| age                  | 1.04 (0.92–1.17)    | 0.53                  |                      |           |
| Child-Pugh score     | 0.99 (0.52–1.88)    | 0.98                  |                      |           |
| ALBI                 | 3.68 (0.72–18.8)    | 0.12                  | 4.39 (0.39–50.0)     | 0.23      |
| FIB-4                | 1.02 (0.84–1.24)    | 0.83                  |                      |           |
| Platelet count       | 20.6 (1.91–209)     | 0.012                 | 21.3 (1.05–435)      | 0.046     |
| Splenic volume       | 0.99 (0.99-1.00)    | 0.04                  | 1.00 (0.99-1.00)     | 0.82      |

ALBI, albumin-bilirubin; FIB-4, fibrosis-4.

Repeated use of lusutrombopag produced the initial response

Because multiple invasive procedures were often needed for patients with liver cirrhosis, lusutrombopag was repeatedly used in 13 patients; 9 patients of these patients received lusutrombopag 3 or more times. The maximum use was 5 times in one patient. The intervals of the use ranged from 35 to 781 days (median 166 days). The 2nd use of lusutrombopag significantly increased the platelet count in all 13 patients (Fig. 2a) and group A (Fig. 2b). The response to lusutrombopag in group B was similar to the initial response (Fig. 2c). Although the maximum platelet count tended to be higher in the 2nd treatment in group A, the difference was not statistically significant. We also investigated 9 patients who received lusutrombopag 3 or more times. In 9 patients, the response to the 3rd treatment was similar to that to the
2nd treatment (Fig. 2d); this was observed in groups A (Fig. 2e) and B (Fig. 2f). Of note, the mean platelet count was > 50,000 /µL at the 3rd treatment in group B, which was in contrast to the initial and 2nd treatments (Fig. 2f). In 4 patients who received lusutrombopag 4 or more times, the 4th and 5th treatments increased the platelet count as much as the initial treatment (data not shown).

**Hepatitis C virus (HCV) infection is likely to reduce the platelet count.**

In one patient in group B, the platelet count restored to ≥ 50,000/ µL following lusutrombopag treatment after the successful eradication of HCV; although the first administration of lusutrombopag soon after a sustained virologic response (SVR) failed to increase the platelet count to ≥ 50,000/µL, the 2nd to 5th treatments succeeded in increasing platelet count to ≥ 50,000/µL. Thus, we investigated the effect of HCV infection on platelet counts. Among 13 patients with chronic HCV infection, 7 received lusutrombopag after achieving an SVR. We noted that 2 patients showed a platelet count of ≥ 50,000/µL at baseline after achieving an SVR. Because the platelet count at baseline was a factor that predicted the response to lusutrombopag (Table 2), we compared the platelet count at baseline and the splenic volume before and after achieving an SVR. The platelet count at baseline significantly increased after achieving an SVR (Fig. 3a). In contrast, the platelet count in the non-SVR group tended to decrease during the study period (Fig. 3b). The splenic volume was not associated with the SVR (Fig. 3c, 3d).

**Safety of lusutrombopag**

No thrombosis was noted in the portal vein after lusutrombopag treatment in the present study. In addition, lusutrombopag was well tolerated and no symptomatic adverse effects were observed during its administration of lusutrombopag. Furthermore, no adverse events were noted in cases in which lusutrombopag was repeatedly used. No hemorrhagic complications occurred during or after the procedure in any group.

**The effect of platelet transfusion on the increase of the platelet count**

Finally, we investigated the effects of platelet transfusion in the past. Among 26 patients enrolled in the present study, 13 patients (50%) had experienced platelet transfusion before lusutrombopag became available. Platelet transfusion was performed approximately 3 years before lusutrombopag treatment. Although platelet transfusion significantly increased the platelet count in comparison to baseline, the mean increase was 4,000/µL (Fig. 4, left panel). There were 8 and 5 patients who had a history of platelet transfusion in groups A and B, respectively. The increase in the platelet count by platelet transfusion was small in both groups (Fig. 4, middle and right panels). Among the 13 patients underwent platelet
transfusion in the past, 8 patients (61.5%) could proceed to invasive procedures without platelet transfusion after lusutrombopag treatment. These data indicate that the ability of platelet transfusion to increase the platelet count is limited in patients with platelet counts of <50,000/µL.

Discussion

In the present study, 73.1% of patients who received lusutrombopag treatment could avoid platelet transfusion before invasive procedures. In addition, the repeated use of lusutrombopag showed similar efficacy to the initial treatment. Furthermore, no serious adverse events were observed during or after lusutrombopag treatment. Thus, lusutrombopag was considered effective and safe for CLD patients with a platelet count of < 50,000/µL.

Although platelet transfusion has traditionally performed to increase platelet counts, we have little information on the platelet count increase in patients with liver cirrhosis. Tripodi et al. reported that platelet transfusion increased the peripheral platelet count by 13,000/µL in patients with liver cirrhosis (20). In the present study, the increase in platelet was 4,000/µL by platelet transfusion before lusutrombopag became available. One of the differences between Tripodi’s study and our study was the time point at which platelets were counted. Tripodi et al. performed the count 1 hour after platelet transfusion whereas we did it on the next day after platelet transfusion. In addition, the amounts of platelets transfused differed, with ≥ 3 × 10^{11} platelets in Tripodi’s study and ≥ 2 × 10^{11} platelets transfused in our study. Hirooka et al. reported that only 5% (1/20) patients who received 10 units (≥ 2 × 10^{11}) of platelets showed a platelet count of ≥ 50,000/µL (19). These data indicate that it is difficult to increase number of platelets to a sufficient level by standard platelet transfusion in patients with liver cirrhosis.

Real-world data showed that 84–96% of patients could avoid platelet transfusion in Japan (11)(12)(13). However, these studies included patients with a platelet count of > 50,000/µL at baseline. Because the characteristics of patients were reported to be a low platelet count at baseline in whom lusutrombopag failed to increase a platelet count of > 50,000/µL, (11)(19), it is reasonable that our study showed a relatively low rate in avoiding platelet transfusion. In clinical trials that restricted enrollment to patients with a platelet count of < 50,000/µL at baseline, 72.5–79.2% of patients avoided platelet transfusion. In addition, 14.6%- 34.1% of patients had a platelet count of < 35,000/µL at baseline (8)(9). The present study restricted the enrolled patients to those with a platelet count of < 50,000/µL at baseline; 73.1% of the patients avoided platelet transfusion and 26.9% of the patients had a platelet count of < 35,000/µL at baseline. Thus, the present study reproduced the results of clinical studies in the real-world setting.

Our study included 13 patients who used lusutrombopag two or more times, and the repeated use of lusutrombopag was found to be effective and safe. Although the 2nd use of lusutrombopag tended to increase the platelet count in comparison to the first treatment, this may depend on the day when platelets were counted. In the first lusutrombopag treatment between 2016 and 2017, we performed invasive procedures at approximately 10–12 days after the initiation of lusutrombopag treatment.
repeated use of lusutrombopag after 2018, the procedures were performed at approximately 13–15 days after the initiation of lusutrombopag. This suggests that the platelet count was determined before it reached the maximum level in the earlier cases (2016–2017).

We noted that the 3rd lusutrombopag treatment increased mean platelet count to ≥ 50,000/µL in group B, in which platelet count was < 50,000/ µL at the first lusutrombopag treatment. There were patients with chronic HCV infection who achieved an SVR in group B. Indeed, the baseline platelet count was significantly elevated in 7 patients after the achievement of an SVR in both groups A and B. Ishizu et al. reported that an SVR can increase the platelet count by reducing the splenic volume (21). However, the mean splenic volume did not decrease, even after the achievement of an SVR in the present study. In fact, the splenic volume increased in 71.4% (5/7) of the patients in the present study, with the exception of two patients with relatively small splenic volumes. This discrepancy may have been due to the difference in the splenic volume at baseline. The medians splenic volume in the present study was 634 ml, while that in Ishizu’s study was 242 ml (21). Thus, other mechanisms accounted for the increased platelet count in group B patients who received repeated treatment. There are several mechanisms by which HCV infection reduces platelet count, including bone marrow suppression and immune dysfunction (22). In fact, patients with a non-SVR tended to show decreased platelet count during the study period. Although we did not examine detail mechanisms related to HCV infection in the present study, our data strongly suggest that chronic HCV infection reduces the platelet count.

Conclusion

Lusutrombopag is effective and safe for CLD patients with a platelet count of < 50,000/µL. Thus, using lusutrombopag, we can perform invasive procedures without platelet transfusion in the majority of patients with severe thrombocytopenia.

Abbreviations

CLD: Chronic liver disease
CT: computed tomography
ALBI: Albumin-Bilirubin
FIB-4: fibrosis-4
HCV: hepatitis C virus
SVR: sustained virologic response

Declarations
Ethic approval and content to participate

This study was approved by the institutional review board of Jichi Medical University (permission number: A20-006) and independent ethics committees of all participating institutions and was conducted in accordance with the Declaration of Helsinki. Because of the retrospective nature of this study, the requirement of written informed consent was waived. Instead, opt-out consent documents were shown on the website of Jichi Medical University for patients who did not wish to participate in the study. The following institutions in Japan participated in the present study; Jichi Medical University, Tochigi Medical Center Shimotsuga, and Haga Red Cross Hospital.

Content for publication

Not applicable

Availability of data and materials

All datasets used and analyzed in the present study are available in Supplemental Table 1

Competing interests

Hironori Yamamoto received research fee from Shionogi & Co., Ltd., Osaka, Japan. Other authors declare that they have no conflict of interest.

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Authors’ contribution

Study design and concept: HN, NM, KM. Data acquisition: HN, NM, KM, SM, YT, HM, TS, YK, HK, NN, NI, Statistical analyses: NM, SW, Drafting manuscript: HN, KM. Critical Revision of the manuscript and supervision: NI, HY

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