Editorial

Real World Data of thrombopoietin receptor for thrombocytopenia with chronic liver disease

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Thrombocytopenia is one of major complication in chronic liver disease patients, with approximately 76% of patients having platelet counts <150,000/μL and approximately 13% having platelet counts between 50,000–75,000/μL (1).

Periprocedural bleeding risk management is an essential strategy in chronic liver disease. Chronic liver disease patients frequently require invasive diagnostic and therapeutic procedures, such as liver biopsies, variceal band ligation, or percutaneous procedures such as radiofrequency ablation and microwave ablation for hepatocellular carcinoma (HCC) (2).

However, these procedures may be delayed or sometimes canceled due to the risk of bleeding in patients who also have thrombocytopenia.

Therefore, thrombocytopenia is a major issue in patients with chronic liver disease.

Historically, the treatment options for thrombocytopenia in chronic liver disease have been platelet transfusions, either immediately before or during the procedure (3,4).

Platelet transfusion has been established is considered the standard of care for managing thrombocytopenia in patients with chronic liver disease (3,4), and is supported by society guidelines, with platelet goals ≥50,000/μL widely recommended for many procedures (3,4).

However, platelet transfusion has many disadvantages, such as increased risk of viral and bacterial infections (5), the development of febrile nonhemolytic reactions such as anaphylactic shock, anaphylaxis, hypotension, dyspnea, transfusion associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI) (6) and non-serious adverse reactions such as urticaria and fever. There are also problems such as the risk of infectious diseases and platelet transfusion refractoriness due to repeated transfusion due to human leukocyte antigen alloimmunization (7).

Recently with the advance in the knowledge of thrombopoiesis and the role of its key regulator, thrombopoietin (TPO) led to the production of novel drugs that act as TPO receptor (TPO-R) agonists that activate and enhance megakaryopoiesis which in turn increase platelet synthesis (8).

Hence, TPO, also known as Megakaryocyte Growth and Development Factor (MGDF) or c-MpL ligand, is a hormone which is synthesized in the liver and dominantly regulates the process of megakaryocytopoiesis (9). TPO acts on c-MpL receptor on the surface of megakaryocytes and stimulates various steps of platelet production within the bone marrow (10). TPO generation in turn is regulated by the rate of platelet cycling (production and destruction), as well as the synthetic function of liver (11). Several studies have argued about the relative majority influence on this multifactorial etiology of thrombocytopenia in CLD (11).

Romiplostim and eltrombopag were developed as successful first generation TPO receptor agonists.

Romiplostim is indicated for thrombocytopenia due to hematologic disorders. Hence, some studies and case

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reports exist in patients with liver disease (2), but safety concerns for portal vein thrombosis (PVT) have been occurred (12).

On the contrary, eltrombopag was previously used in patients receiving interferon treatment for hepatitis C when thrombocytopenia otherwise limited treatment (13). the trial conducted to evaluate the efficacy of eltrombopag for patients with chronic liver disease that need to undergo the invasive procedure was discontinued due to increased risk of thromboembolic events (14).

The risk of occurrence of PVT (13) and hepatotoxicity, eltrombopag is no longer commonly used in patients with liver disease. Furthermore, re-administration may increase the platelet count excessively, thus increasing the risk of thromboembolism as eltrombopag in ELEVATE study (14).

Hence, two nonpeptide TPO agonists as new second generation TPO agonists, avatrombopag and lusutrombopag, were recently approved to provide an alternative for the management of thrombocytopenia associated with chronic liver disease who undergo elective procedures.

Avatrombopag is an orally administered, small nonpeptide second generation TPO receptor agonist that is shown to mimic the biological effects of TPO both in vitro and *in vivo*. It is being utilized in clinical trials including patients with chronic immune thrombocytopenic purpura (ITP) (15) and for chronic liver disease (16).

As with all TPO agonists, there is a potential risk of thromboembolism that must be monitored in terms of using avatrombopag. In ADAPT-1 and ADAPT-2, adverse effects including PVT were uncommon (16). Verma *et al.* revealed that avatrombopag is a safe and effective alternative to platelet transfusion to treat thrombocytopenia in patients with chronic liver disease scheduled to undergo a procedure in real world study (17).

This study revealed that the most common indication for avatrombopag was esophagogastroduodenoscopy (EGD) with planned esophageal band ligation (86%). Platelet count increased 2.2 folds, from 37,400/mL to 76,900/mL in 20 patients who had peri-procedure platelet counts. Furthermore, no patients required rescue therapy or platelet transfusion and there were no adverse effects. Verma *et al.* also proved that there was no new PVT (17).

Hence, lusutrombopag (Shionogi & Co., Ltd., Osaka, Japan) has been approved in Japan for the improvement of chronic liver disease-associated thrombocytopenia in patients scheduled to undergo invasive procedures (18). It is a chemically synthesized, orally active, small molecule human TPO receptor agonist that activates the signal transduction pathway in the same fashion as endogenous TPO and induces platelet production (19).

A Japanese phase III trial examined the effect of lusutrombopag administration prior to invasive procedures in Japanese patients with chronic liver disease, and it demonstrated that lusutrombopag administration resulted in avoidance of platelet transfusion in a significantly higher proportion of patients than in those on placebo (79.2% and 12.5%, respectively) (19).

Phase II and phase III trials demonstrated that the platelet count was maintained at ≥ 50,000/μL for a median of 21.0 and 22.1 days, respectively, in patients who were on lusutrombopag and did not require platelet transfusion (20).

TPO agonists are effective in increasing platelet count for a longer duration than platelet transfusions. Platelet counts rapidly rise after 5 days of avatrombopag, peak at day 10, and return to baseline levels by about 1 month (15,16). For lusutrombopag, the median duration of platelet counts remaining ≥50,000/μL is 19-22 days (20).

Due to longer lasting rise effects in platelets, these second generation TPO agonists can allow either repetition of procedures or postponement without repeat dosing.

Moreover, both agents are metabolized primary by the hepatic cytochrome p450 system. Avatrombopag was studied in patients with cirrhosis with Child Pugh classes A, B, and C with Model for End-Stage Liver Disease (MELD) scores of ≤23 (15,16). However, no hepatic dose adjustment according to hepatic function is needed.

Lusutrombopag was studied in patients with cirrhosis with Child Pugh classes A and B and also requires no hepatic dose adjustment according to hepatic function. As for renal function, in patients with concomitant mild or moderate renal disease [creatinine clearance (CrCl) >30 mL/minute], neither avatrombopag nor lusutrombopag require renal dose adjustment according to renal function (19,20). Hence, insufficient data exist for use of these agents in patients with CrCl <30 mL/minute.

Furthermore, neither avatrombopag nor lusutrombopag was studied for use in the pediatric population (16,19,20). There are insufficient data to inform pregnancy risks; animal studies suggest potential fetal harm at highly supratherapeutic doses (16,18-20). Neither is recommended for use in lactating women.

Avatrombopag is dispensed in 20 mg tablets, and dosing is determined by baseline platelet count; 40 mg is used if platelets are 40,000–49,000/μL, and 60 mg is used if platelets are <40,000/μL (16). Each dose is taken once daily

for 5 days and should be started 10–13 days before the scheduled procedure (15,16). The procedure should then be completed 5–8 days after the last dose per prescribing guidelines (16).

Lusutrombopag is dispensed in 3-mg oral tablets and is a uniform dose regardless of baseline platelet count (19,20). It is administered once daily with or without food for 7 days before a procedure, which should be performed 2–8 days after the last dose per prescribing guidelines (19,20). However, procedure timing is at the discretion of the providers and could be performed outside these studied time windows if the platelet count is above the goal.

Hence, patients with chronic liver disease often require repeat invasive procedures.

It is important to analyze the treatment effect and safety of repeated use TPO receptor agonists.

Saab *et al.* reported that repeat use of avatrombopag continues to be an effective tool to minimize the use of platelet transfusions in patients undergoing invasive procedures who have chronic liver disease. Moreover, they reported that repeat dosing does not appear to reduce avatrombopag (21).

Avatrombopag repeated indication were all esophago-gastro-duodenoscopy (EGD) with planned esophageal band ligation (21).

As for lusutrombopag, repeated use of lusutrombopag increased the platelet count. It did not cause any serious adverse events and led to avoidance of platelet transfusion. Radiofrequency for HCC was performed safely in all patients at the time of repeat RFA were investigated in patients with recurrent HCC and thrombocytopenia (22).

Future studies with more cases of repeated use are needed to examine the long-term efficacy and safety of avatrombopag and lusutrombopag.

Moreover, it is also necessary to consider how to use each TPO agonists such avatrombopag and lusutrombopag according to the therapeutic procedure for thrombocytopenia with chronic liver disease (23,24).

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