MANAGEMENT OF THROMBOCYTOPENIA IN CIRRHOSIS

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Key Concepts
• Definition of thrombocytopenia
• Causes of thrombocytopenia
• Pharmacologic treatment of thrombocytopenia
• Surgical treatment of thrombocytopenia

Abstract: Thrombocytopenia is a common complication in liver disease, and liver disease-related thrombocytopenia is often defined as a platelet count < 100 × 10^9/L, including moderate (less than 100 × 10^9/L) and severe (less than 50 × 10^9/L) thrombocytopenia. The presence of thrombocytopenia can aggravate surgical or traumatic bleeding and can also significantly complicate routine patient care, such as liver biopsy, antiviral therapy, and medically indicated or elective surgery for cirrhotic patients, resulting in delayed or cancelled medical management and affecting the administration of effective treatment for several conditions. Multiple factors, including splenic sequestration, reduced activity of the hematopoietic growth factor thrombopoietin (TPO), cirrhotic coagulopathy, cirrhotic bone marrow suppression by chronic HCV infection and anti-cancer agents, and antiviral treatment with interferon (IF-N)-based therapy, can contribute to the development of thrombocytopenia in cirrhotic patients.

Key words: Thrombocytopenia, Thrombopoietin, Promegapoitein, Danazol.

Thrombocytopenia is a common complication in liver disease, and liver disease-related thrombocytopenia is often defined as a platelet count < 100 × 10^9/L, including moderate (less than 100 × 10^9/L) and severe (less than 50 × 10^9/L) thrombocytopenia. Although clinically significant spontaneous bleeding does not usually occur until the platelet count is less than 10 × 10^9/L-20 × 10^9/L, cirrhotic patients with or without cancers often require numerous medical and/or surgical procedures during diagnosis and therapy. The presence of thrombocytopenia can aggravate surgical or traumatic bleeding and can also significantly complicate routine patient care, such as liver biopsy, antiviral therapy, and medically indicated or elective surgery for cirrhotic patients, resulting in delayed or cancelled medical management and affecting the administration of effective treatment for several conditions (e.g., antiviral therapy for chronic hepatitis C virus (HCV) infection or cancer chemotherapy). Indeed, the degree of thrombocytopenia has been shown to be a useful prognostic marker in cirrhotic patients because the finding of severe thrombocytopenia (< 50 × 10^9/L) in liver disease can be associated with significant morbidity. Additionally, a decreased platelet count can often be a diagnostic clue.
to unsuspected cirrhosis and to the presence of esophageal varices\textsuperscript{3-6}. Multiple factors, including splenic sequestration, reduced activity of the hematopoietic growth factor thrombopoietin (TPO), cirrhotic coagulopathy, cirrhotic bone marrow suppression by chronic HCV infection and anti-cancer agents, and antiviral treatment with interferon (IFN)-based therapy, can contribute to the development of thrombocytopenia in cirrhotic patients. Of these factors, the major mechanisms for thrombocytopenia in liver cirrhosis are\textsuperscript{1} platelet sequestration in the spleen; and\textsuperscript{2} decreased production of TPO in the liver. Historically, thrombocytopenia has been thought to arise from the increased pooling of platelets in an enlarged spleen (splenomegaly). While the normal splenic volume has been reported to range from 50-200 mL\textsuperscript{7}, splenomegaly sometimes increases it to even more than 1000 mL. Platelet sequestration is seen in congestive splenomegaly due to cirrhosis-induced portal hypertension and is characterized by a redistribution of platelets from the circulating pool to the splenic pool\textsuperscript{8}. However, the interventional and/or surgical treatments aimed at reversing portal hypertension do not always correct thrombocytopenia in the clinical setting. Indeed, decreased platelet production has been noted, even in patients without splenomegaly\textsuperscript{9}, suggesting that other factors are involved in thrombocytopenia due to liver cirrhosis. Platelets are derived from megakaryocytes, and TPO is known to be a potent cytokine that regulates megakaryocyte and platelet production\textsuperscript{10-11}. TPO, which is primarily produced in the liver but is also produced, to a lesser extent, in the bone marrow and kidney\textsuperscript{12-13}, binds to the TPO receptor (c-Mpl), which is expressed on the surface of stem cells, megakaryocyte progenitor cells, megakaryocytes, and platelets. Experimentally, when TPO or its receptor (c-Mpl) has been “knocked-out” by homologous recombination in mice, the megakaryocyte and platelet masses are reduced to approximately 10% of the normal value, even though the animals are healthy and do not spontaneously bleed\textsuperscript{14-16}. Cirrhotic patients with thrombocytopenia have lower circulating TPO levels than do cirrhotic patients with normal platelet counts, possibly as a result of diminished TPO production\textsuperscript{17}. Interestingly, following successful liver transplantation or splenic embolization, the TPO levels appear to normalize, suggesting that decreased TPO production in the liver may also contribute to thrombocytopenia in cirrhotic patients\textsuperscript{17-19}.

**Treatment.**
The most practical strategy in treating HCV-related thrombocytopenia is based on the principle that eradication of HCV infection should result in remission of thrombocytopenia. Thus the usual protocol to treat HCV-related thrombocytopenia is to continue with IFN therapy but reduce its dose if platelet count falls to <30,000 cells/µL or discontinue the dose if it falls to <20,000 cells/µL\textsuperscript{20,21}. The minimum effective dose of PEGINF appears to be 1 µg/kg/week. If platelet counts of <30,000 cells/µL persist even after reducing PEG-IFN dose to the minimum effective level, initiating some adjunct therapy such as eltrombopag may be considered\textsuperscript{22}.

**Pharmacological treatment**

**Steroids**
The use of steroid therapy in the management of HCV-related thrombocytopenia has never gained popularity because despite conflicting reports of variable increase in platelet counts, steroid therapy has shown to cause a rise in transaminase levels and HCV viral load, and worsening of liver damage. Steroids have even shown to cause an eleva-
tion in serum bilirubin levels and development of overt jaundice.\textsuperscript{23}

**Platelet transfusions**
Platelet transfusion does not always ensure maintenance of adequate platelet levels, and patients are at risk for serious transfusion-related complications including viral or bacterial infection, alloimmunization and febrile non-hemolytic reactions following repeated transfusions.\textsuperscript{24-25} Platelet transfusion complications occur in up to 30\% of patients. The most common adverse event is the development of “refractoriness”, occurring in approximately 50\% of all patients undergoing multiple platelet transfusions.\textsuperscript{26} Refractoriness typically arises from human leukocyte antigen alloimmunization and non-immune platelet consumption associated with splenomegaly, disseminated intravascular coagulation and septicaemia.\textsuperscript{27}

The use of prophylactic platelet transfusions is controversial in many patients. Additionally, platelet transfusion is generally not necessary for uncomplicated patients without liver disease and those with platelet counts >20,000 cells/µL.\textsuperscript{28} For patients with platelet counts <20,000 cells/µL, platelet transfusions are given or the planned medical procedure is postponed.\textsuperscript{29} Patient populations at higher risk for bleeding complications, including surgical patients and those with infection or splenomegaly, may warrant higher cutoff values of 50,000–100,000 cells/µL.\textsuperscript{30} Platelet transfusions are not indicated prior to anti-HCV therapy or during therapy unless patients have active bleeding with platelet counts <50,000 cells/µL.

**Targeting general thrombopoiesis: cytokines and growth factors**

**Thrombopoietin**
Thrombopoietin is a potent megakaryocyte colony-stimulating and maturation factor, shown to induce colony formation from as many as two thirds of all megakaryocyte progenitors. Although thrombopoietin has profound effects on the proliferation and maturation of megakaryocytes,\textsuperscript{31} its effects on the release of platelets from the mature megakaryocyte are less significant.

High levels of thrombopoietin activate megakaryocyte production, increasing the number of platelets, thereby normalizing thrombopoietin levels through feedback regulation. When liver function is impaired (e.g. due to cirrhosis), thrombopoietin secretion decreases, which results in a reduction in platelet counts.\textsuperscript{32-33}

Two forms of recombinant thrombopoietin have been evaluated in clinical trials. Although both produced a dose dependent increase in platelet counts in healthy volunteers and cancer patients, their clinical development was halted because of adverse effects as thrombocytopenia and pancytopenia from the generation of neutralizing antibodies to thrombopoietin.\textsuperscript{34-35} However, clinical development of these compounds did provide important clinical proof-of-principle for the use of thrombopoietin agonists in the treatment of various types of thrombocytopenia. IL-1, IL-3, IL-6, and GM-CSF In animals, IL-1, IL-3, IL-6 and granulocyte macrophage-colony stimulating factor (GM-CSF) have been shown to play a role in the generation of megakaryocytes and have shown thrombopoietic activity in clinical studies. However, these compounds resulted in unacceptable toxicity profiles or did not produce significant increases in platelet counts. These find-
ings led to the discontinuation of research on possible therapeutic uses of these cytokines for the treatment of thrombocytopenia.\textsuperscript{36}

\textbf{Promegapoietin}

Promegapoietin, a thrombopoietin/IL-3 chimeric molecule, was engineered based on the synergy of IL-3 and thrombopoietin on megakaryocyte proliferation and maturation. When administered in a primate model of severe radiation-induced myelosuppression, platelet regeneration was restored, virtually eliminating the need for whole blood transfusions.\textsuperscript{37} However, in a phase 1 clinical study, antibody formation resulted in severe thrombocytopenia, terminating further development of promegapoietin.\textsuperscript{38}

\textbf{IL-11}

In vitro, IL-11 works synergistically with other cytokines to promote multiple stages of megakaryocyte development. Megakaryocytes and megakaryocyte precursors express IL-11 receptors. IL-11 promotes megakaryocyte maturation, stimulates platelet production, and can enhance hematopoietic recovery following myelosuppression. Clinically, recombinant human IL-11 (rhIL-11; oprelvekin) has been successful in some specific patient groups. In a phase 1 study in patients with advanced breast cancer treated with myelosuppressive chemotherapy, treatment with rhIL-11 produced dose-dependent increases in bone marrow progenitor cells, megakaryocytes and platelets.\textsuperscript{39} In a randomized, placebo controlled trial in patients with solid tumours who were severely thrombocytopenic because of myelosuppressive chemotherapy and had previously received platelet transfusions, treatment with oprelvekin provided positive results to support approval for the indication of chemotherapy-induced thrombocytopenia. Adverse events associated with IL-11 include oedema, fluid retention, and less frequently, cardiac arrhythmia and syncope. The adverse event profile and the modest improvement of platelet counts have limited the use of this agent for its approved indication. One case study has shown that oprelvekin can correct HCV-associated thrombocytopenia, raising the possibility that the compound could allow some HCV-infected patients with low platelet counts to complete antiviral therapy.\textsuperscript{40} However, oprelvekin is not currently approved for chronic liver disease-related thrombocytopenia.

Targeting thrombopoietin receptor activation: thrombopoietin agonists

\textbf{Eltrombopag}

Eltrombopag, an orally bioavailable, non-peptide growth factor, is a selective thrombopoietin receptor (Mpl) agonist. It interacts with the transmembrane domain of Mpl, rather than the ligand binding domain of the receptor, leading to activation of the JAK/STAT and MEK/ERK signalling pathways. In initial studies, it has been found to be well tolerated and associated with dose-dependent increases in circulating platelet counts.\textsuperscript{41-42} A randomized, double-blind, placebo-controlled phase 2 study, evaluated whether eltrombopag could facilitate initiation and maintenance of interferon-based antiviral therapy in patients with thrombocytopenia associated with chronic HCV infection.\textsuperscript{43} The initial eltrombopag pretreatment resulted in significant increases in platelet counts at week 4 in all treatment groups. The number of patients able to initiate antiviral treatment ranged from 71\% to 91\% with eltrombopag vs. 22\% in the control arm. In total, 65\% of patients in the 75 mg dose group, 53\% of patients in the 50 mg dose group, and 36\% of patients in the
30 mg dose group were able to complete the 12-week antiviral therapy phase compared to 6% of placebo-treated patients (p<0.001, p not provided, and p=0.003, respectively). Eltrombopag treatment was generally well tolerated. The most frequent adverse events during the eltrombopag-only pretreatment phase were nausea, headache and dry mouth, none of which required treatment discontinuation. Pivotal phase 3 studies are under way to further examine eltrombopag in patients with chronic HCV infection with associated thrombocytopenia. Eltrombopag has also been reported to increase platelet counts in patients with chronic idiopathic thrombocytopenic purpura (ITP).  

Romiplostim
Romiplostim is a thrombopoietin peptide agonist consisting of two Fc fragments (a human IgG1 heavy chain disulphide bonded to a kappa light chain) each covalently linked to two identical peptide sequences that could bind to Mpl. To design a compound with a reduced likelihood of an anti-thrombopoietin immune response that would still bind and activate Mpl, the peptide sequence was identified by screening peptide libraries with no sequence homology to human thrombopoietin. Romiplostim was found to bind to Mpl, induce the phosphorylation of JAK2 and STAT5, promote the growth of thrombopoietin-dependent cell lines and the development of megakaryocyte colonies, and increase in vitro megakaryocyte ploidy and maturation. Romiplostim has not been tested in patients with chronic liver disease or HCV infection, but treatment with romiplostim has been shown to increase platelet counts in other patient populations. Phase 1 studies in both normal healthy subjects and patients with ITP revealed that single subcutaneous injections of romiplostim gave rise to a dose-dependent increase in platelet count, starting at day 5 and peaking at days 10–15.47 A subsequent phase 2 study in patients with ITP showed that once-weekly doses of romiplostim resulted in a platelet response in 31 of 36 patients.48

In August 2008, the US FDA approved romiplostim for adult patients with chronic ITP. The approval was based on the efficacy and safety results of two open-label phase 3 studies in patients receiving treatment for 24 weeks. The overall response rate for romiplostim was 83%. Additionally, patients treated with romiplostim were significantly less likely than placebo-treated patients to require treatment with rescue or emergency medications (corticosteroids, intravenous immunoglobulin, intravenous Rho(D) immunoglobulin, anti-D therapy). Safety data from these studies indicate that romiplostim is well tolerated, with no serious adverse events.49-50 An alternate approach to the treatment of thrombocytopenia is the use of agonist antibodies, which are thought to dimerize and activate thrombopoietin via their bivalent binding properties. These engineered antibodies are not orally available but have long circulating half-lives that may show therapeutic utility following single doses. Monoclonal antibodies that bind Mpl have been modified to create small, bivalent thrombopoietin agonist “minibodies” that activated a thrombopoietin-expressing cell line and were able to induce phosphorylation of JAK2, STAT5 and Mpl as potently as rhTPO.51 The administration of such minibodies to cynomolgus monkeys increased platelet counts.52

Danazol
Danazol therapy was useful and well tolerated when used for treatment of refractory au-
to immune thrombocytopenia with unknown mechanism.\textsuperscript{53-54} It has been shown that danazol therapy modifies the level of antiplatelet antibodies and inhibits the mononuclear phagocyte system in patients with refractory thrombocytopenia.\textsuperscript{55-56} In a recent study, danazol was used in patients with thrombocytopenia associated with HCV infection during pegylated interferon plus ribavirin therapy. The study included 49 patients receiving pegylated interferon plus ribavirin therapy and danazol. There was increase in platelet count to >100,000 cells/µL in 10.6% of cases and 71% of them maintained their initial platelet counts.\textsuperscript{57} Further studies are needed to clarify the role of danazol in patients with thrombocytopenia.

**L-carnitine**

L-carnitine (4-N-trimethyl ammonium 3-hydroxybutyric acid) is a conditionally synthesized nutrient from the amino acids lysine and methionine in the human liver, brain and kidney, but is largely obtained from meat and dairy products. Recently, L-carnitine has been proposed as a potential adjuvant treatment to improve anaemia, thrombocytopenia, leukopenia and immunological function.\textsuperscript{58-59} In a recent study, L-carnitine added to Peg-IFN-a plus ribavirin led to less decrease of platelet count during antiviral therapy.\textsuperscript{60} Some studies indicate that L-carnitine modulates platelet functions and production through antioxidant mechanisms and the inhibition of the arachidonic acid cascade.\textsuperscript{61-62} Arachidonic acid has a key role in the activation of blood platelets and in the formation of free radicals via the stimulation of NADPH oxidase in these cells. L-carnitine interfering with arachidonic acid metabolism has a direct effect on platelet activation and oxidative stress. It inhibits platelet superoxide anion formation elicited by arachidonic acid and collagen, but has no effect on thrombin-induced platelet aggregation.\textsuperscript{63}

Non-pharmacological treatment.

**Splenectomy**

Splenectomy and splenic artery embolization have been used to correct thrombocytopenia in patients with hypersplenism, producing significant and persistent increases in platelet counts. Splenectomy has shown to produce comparable responses in HCV-positive and HCV-negative chronic ITP cases.\textsuperscript{64-65} Although successful results have been reported, splenectomy is potentially associated with multiple complications. It is an invasive procedure that can be technically difficult, with a high risk of bleeding in patients with portal hypertension, varices, and enlarged spleen. Portal vein thrombosis and pancreatic leaks requiring surgical reexploration have been described as complications.\textsuperscript{66-67}

Splenectomy also places patients at risk for overwhelming post splenectomy sepsis syndrome (OPSS), usually due to encapsulated organisms. Splenic artery embolization decreases the morbidity and mortality associated with splenectomy but is not without risks.

**Partial splenic embolization (PSE)**

Partial splenic embolization (PSE) is a non-surgical, less invasive treatment of hypersplenism. It is usually performed via a percutaneous femoral artery approach. The embolization catheter is advanced into the splenic hilum as far as possible in order to avoid injury to the pancreatic circulation. Gelatin sponge slurry suspended in an antibiotic solution, coils, microspheres, and polyvinyl alcohol particles are used for embolization of approximately 60\%-70\% of spleen pa-
renchyma. Splenic embolization procedures date back to the year 1973, when the entire spleen parenchyma was ablated. At that time the procedure was associated with high rates of complications, including splenic abscesses, rupture, and pancreatic infarction resulting in a high mortality rate. In several reports in the literature, PSE has been described in patients after liver transplantation. It has been successful in patients with thrombocytopenia and recurrent HCV infection who were able to undergo treatment with interferon and ribavirin as a result of ablation.68-69

Many patients develop post-embolization syndrome, including symptoms of fever, left upper quadrant pain, pleural effusion, pneumonia, and atelectasis. Splenic abscesses and rupture are infrequent and are more commonly encountered and less tolerated by immunocompromised cirrhotic patients with a greater area of embolization.70 The risk is greatly reduced with aseptic technique, antibiotic prophylaxis, and careful control of pain. Extent of embolization is important as well, with more complications following greater than 70% area of ablation. In PSE, achieving the intended target embolization area remains a challenge. Graded PSE at several settings has been entertained in order to avoid excessive embolization and severe complications associated with it.71

PSE is minimally invasive and effective for thrombocytopenia caused by hypersplenism and improving liver function. PSE not only increased platelet counts, facilitating the adherence to Peg-IFN therapy in patients with chronic HCV infection associated with thrombocytopenia but also significantly reversed insulin resistance in patients with liver cirrhosis. The increase in intestinal venous flow to the liver and reduced HCV viral load were thought to be the mechanisms of improvement in insulin sensitivity after PSE.72-73

**Transjugular intrahepatic portosystemic shunt (TIPS)**

TIPS is used to decrease sinusoidal portal pressure in patients with cirrhosis and to manage complications of portal hypertension, such as recurrent variceal haemorrhage and ascites.74-75 When performed by experienced physicians, TIPS is typically a safe procedure, shown to increase platelet counts in some patients. However, in most cirrhotic patients, TIPS does not result in reliable increases in platelet counts and therefore cannot be recommended as a therapy for thrombocytopenia in such patients. The limitations of splenic artery embolization and TIPS (e.g. significant cost, not universally available, uncertain long-term benefit, and risk of complications, such as hepatic encephalopathy) limit their use in chronic liver disease.76

**Summary**

In patients with chronic HCV infection, thrombocytopenia may represent an obstacle to invasive diagnostic or therapeutic procedures and anti-viral treatment. Management options include pharmacological and non-pharmacological treatment. Indeed, pharmacologic treatment options for thrombocytopenia can be divided into treatments targeted at the thrombopoietin receptor (synthetic thrombopoietins and thrombopoietimimetic agents), and use of cytokines with general thrombopoietic potential. Unfortunately, use of synthetic thrombopoietin was hampered by the development of neutralizing antibodies, thrombopoietin-mimetic agents need further large clinical studies and cytokines are still under trials. Small studies denoted a possible role of danazol and L-carnitine in the treatment of HCV-as-
sociated thrombocytopenia. PSE represent a safe and effective non-pharmacological treatment option replacing splenectomy for thrombocytopenia.

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