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Review article: thrombocytopenia in chronic liver disease

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SUMMARY

Background
Thrombocytopenia is a common finding in advanced liver disease. It is predominantly a result of portal hypertension and platelet sequestration in the enlarged spleen, but other mechanisms may contribute. The liver is the site of thrombopoietin (TPO) synthesis, a hormone that leads to proliferation and differentiation of megakaryocytes and platelet formation. Reduced TPO production further reduces measurable serum platelet counts.

Aim
This paper describes the scope of thrombocytopenia in chronic liver disease and assesses the clinical impact in this patient population.

Methods
A medline review of the literature was performed pertaining to thrombocytopenia and advanced liver disease. This data is compiled into a review of the impact of low platelets in liver disease.

Results
The incidence of thrombocytopenia, its impact on clinical decision making and the use of platelet transfusions are addressed. Emerging novel therapeutics for thrombocytopenia is also discussed.

Conclusions
Thrombocytopenia is a common and challenging clinical disorder in patients with chronic liver disease. New therapeutic options are needed to safely increase platelet counts prior to invasive medical procedures as well as to counteract therapies that further exacerbate low platelets, such as interferon. An ideal compound would be orally available and safe, with rapid onset of action.

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INTRODUCTION

Patients with chronic liver disease including advanced fibrosis and cirrhosis commonly experience thrombocytopenia. In the United States, approximately 8 million units of platelets are transfused each year to reduce the risk of bleeding.[1] Thrombocytopenia associated with chronic liver disease has been reported in 15–70% of patients with advanced fibrosis and portal hypertension, depending on the stage of disease and the platelet cut-off level used to define thrombocytopenia.[2, 3] Thrombocytopenia may be caused by hepatitis C virus (HCV) directly,[4, 5] or it may result from interferon (IFN)-based anti-viral therapy that affects platelet number or function, either directly or by suppression of thrombopoiesis in the bone marrow.[6, 7] Although thrombocytopenia is typically low grade and not life-threatening, extended or severe thrombocytopenia is associated with a poor clinical outcome because it increases the risk of bleeding from invasive procedures,[8, 9] complicates therapy[6, 10] and increases the risk of mortality.[3]

Standard therapy for thrombocytopenia consists of platelet transfusions. Although advances have been made in platelet collection, storage and transfusion, patients are still at risk for complications including infection, alloimmunization and febrile non-haemolytic reactions.[11, 12] Other methods for treatment of thrombocytopenia, including splenic artery embolization, transjugular intrahepatic portosystemic shunts (TIPS) and splenectomy, are also associated with significant risks.[13, 14] Moreover, these approaches are invasive, costly and not always suitable for patients with advanced liver disease.

Effective management of thrombocytopenia may help prevent the postponement or cancellation of other medically necessary procedures from risk of bleeding complications, and may allow initiation of HCV anti-viral therapy. Effectively managing thrombocytopenia may also reduce healthcare costs for patients with chronic liver disease and improve patient outcomes. Because of the limitations of platelet transfusions in the treatment of thrombocytopenia, novel therapeutic approaches are being evaluated. In this review, the scope and impact of thrombocytopenia in chronic liver disease are highlighted. Traditional therapies and their limitations in this type of patient population are also discussed.

INCIDENCE OF THROMBOCYTOPENIA

Patients with advanced chronic liver disease frequently experience thrombocytopenia with increasing incidence correlating with severity of liver disease.[5] In cirrhotic patients, thrombocytopenia occurs in up to 64% of patients and is independent of the cause of cirrhosis.[2] Patients with more advanced end-stage disease tend to have a higher degree of thrombocytopenia than those with compensated chronic liver disease.[15]

Platelet counts of <150 000/μL are more frequently observed in patients with cirrhosis compared to patients without cirrhosis (64% vs. 6%, respectively);[2] approximately one-quarter to one-half of cirrhotic patients have counts <100 000/μL.[2, 16] Platelet counts <50 000/μL occur in approximately 1% of patients with chronic HCV infection.[2]

IMPACT OF THROMBOCYTOPENIA ON CLINICAL MANAGEMENT

The inability to initiate or maintain planned treatments because of low platelet counts may lead to increased morbidity or mortality, and can significantly impact patient care. Many doctors will not initiate HCV anti-viral therapy if platelet counts are low. Postponement of treatment due to thrombocytopenia can result in diminished sustained virological response and the need for additional therapies.[17] Recently issued treatment guidelines by the American Gastroenterological Association suggest that patients with severe thrombocytopenia should not receive IFN-based anti-viral therapy.[10] Initiation of anti-viral therapy is generally contraindicated when platelet counts are below 75 000–100 000/μL,[18] although actual clinical practice may vary. Product labels for pegylated (PEG)-IFN recommend dose reductions for patients with platelet counts between 50 000 and 100 000/μL and suspending therapy if platelet counts fall below 25–50 000/μL.[10] In addition, treatment with PEG-IFN has been shown to reduce platelet counts by up to 33%.[19]

Patients with chronic liver disease frequently undergo medical procedures for diagnosis and treatment, some of which are invasive. Thrombocytopenia can complicate or postpone routine care by increasing the risk of bleeding from such procedures. These procedures include liver biopsies (percutaneous, laparoscopic and transjugular);[1, 9, 20, 21] banding; paracentesis and

thoracentesis for ascites;[22–24] liver transplantation;[25] central line insertion; endoscopy; prostate biopsy and elective surgery. Some studies have found no increase in the risk of bleeding in patients with platelet counts above 50 000/μL undergoing these procedures.[26–30] Many doctors may avoid or postpone procedures until platelet counts increase to near-normal levels on account of the questionable safety of these procedures in chronic liver disease patients with reduced platelet counts and the concern over haemorrhage.[3, 9] Dental procedures, such as extraction, may also be rescheduled due to fear of potential bleeding in patients with severe thrombocytopenia.[8] The risk of bleeding complications can cause postponement of necessary procedures and therapy, interfere with planned medical care, significantly add to healthcare costs in these patients.

TRIGGER FOR PLATELET TRANSFUSION IN THROMBOCYTOPENIA

Prophylactic platelet transfusion is often performed for thrombocytopenic patients who are at increased risk of bleeding during planned invasive procedures. The platelet count at which transfusions are indicated is controversial, especially in patients with chronic liver disease. For uncomplicated patients (without liver disease) with platelet counts >20 000/μL, platelet transfusion is generally not necessary.[31] For patients with platelet counts <20 000/μL, platelet transfusions are given or the planned medical procedure is postponed.[31] Some clinicians support reducing the trigger for transfusions to 10 000/μL in patients not at risk for haemorrhage, because in some studies an increase in bleeding complications was not observed.[32, 33] The actual cut-off value has varied in the published literature according to the patient population and the perceived risk of the planned procedure but this issue has not been thoroughly examined in patients with liver disease. Patient populations at higher risk for bleeding complications, including surgical patients and those with infection or splenomegaly, may warrant higher triggers of 50 000–100 000/μL.[32, 33]

Guidelines for platelet transfusion have been issued by several groups, including the American Society of Clinical Oncology, British Committee for Standards in Haematology, College of American Pathologists and the American Society of Anesthesiologists.[34, 35] Higher limits have been proposed for patients at greater risk, such as thrombocytopenia secondary to massive transfusion (50 000/μL), neonatal alloimmune thrombocytopenia (50 000/μL), invasive procedures in cirrhotic patients (50 000/μL) and liver biopsy (50 000–100 000/μL).[35] However, in many cases, formal guidelines are lacking, and the safety of these procedures in patients with substantially lower platelet counts (<20 000/μL) has not been established. It is also not always possible to predict which patients will develop severe thrombocytopenia periprocedurally. Moreover, the relevance of these guidelines for patients with chronic liver disease is unclear. Because of the lack of formal guidelines for patients with chronic liver disease and the increased risk of bleeding with concomitant coagulopathy in this population, all chronic liver disease patients could potentially benefit from therapies that would increase platelet levels to >100 000/μL.

STANDARD TREATMENT OF THROMBOCYTOPENIA

Platelet transfusion has generally been considered the 'gold standard' for treatment of thrombocytopenia as it can correct low platelet counts and reduce the risk of bleeding. Though widely used, this approach has several limitations, particularly for patients with chronic liver disease. Transfusion does not always ensure maintenance of haemostatic platelet levels.[34] While advances have been made in platelet collection, storage and transfusion, patients are still at risk for transfusion-related complications including viral or bacterial infection, alloimmunization and febrile non-haemolytic reactions, following repeated transfusions.[12] Such complications occur in up to 30% of patients undergoing platelet transfusions.[36] The most common complication is the development of refractoriness, occurring in approximately half of all patients undergoing multiple platelet transfusions.[11] Refractoriness typically arises from human leucocyte antigen (HLA) alloimmunization and non-immune platelet consumption associated with splenomegaly, disseminated intravascular coagulation (DIC) and septicaemia.[11] Alloimmunized refractory patients require HLA-matched platelet transfusions, which further increases treatment costs.

Other methods used to treat severe thrombocytopenia include splenic artery embolization, splenectomy and the introduction of a TIPS. Splenectomy and splenic artery embolization have been used successfully to correct thrombocytopenia in patients with

hypersplenism, producing significant and persistent increases in platelet count.[37–40] Used prophylactically, splenic artery embolization can improve thrombocytopenia in patients with HCV-induced cirrhosis and hypersplenism, thus facilitating anti-viral therapy.[41, 42] This technique decreases the risk of sepsis, mortality and other complications that can occur with splenectomy. However, this procedure is not without risk. Splenic abscesses are a known complication.

A TIPS is often used to decrease sinusoidal portal pressure in patients with cirrhosis, and to manage complications including recurrent variceal haemorrhage and ascites.[13, 43, 44] In experienced hands, TIPS is usually a safe and successful procedure. In one study of 23 patients (including 21 cirrhotic patients) undergoing TIPS, patients experienced significant increases in platelet counts (from 86 000 to 135 000/μL), although this was accompanied by significant transient haemolysis.[13] Potential drawbacks of TIPS include hepatic encephalopathy and poor long-term patency, necessitating careful monitoring.[14] In cirrhotic patients, portal decompression by TIPS did not produce reliable increases in platelet levels, and therefore cannot be recommended as a means of correcting thrombocytopenia.[13, 45]

The limitations of splenic artery embolization and TIPS (e.g. significant cost, risk of complications and uncertain long-term benefit) restrict the use of these approaches in patients with liver disease. In addition, these two therapies have produced little to no effect on impaired thrombopoiesis in the bone marrow and are invasive and therefore, not always suitable for patients with advanced liver disease.

NOVEL THERAPIES FOR THROMBOCYTOPENIA

In light of the limitations of standard therapy, better approaches are clearly needed for the treatment of thrombocytopenia associated with chronic liver disease, especially in patients who may not be good candidates for platelet transfusions. Ideally, therapies should increase platelet counts thereby decreasing the need for platelet transfusions, demonstrate activity in the majority of treated patients, have minimal toxicity, and be cost-effective (Table 1).

Recent studies have led to the identification and characterization of molecules that play a key role in the regulation of thrombopoiesis. Research on thrombopoiesis has elucidated the central role that thrombopoietin (TPO) plays in regulating megakaryocyte maturation and platelet production.[11] Novel agents are being developed that target the thrombopoietic pathway in an attempt to stimulate thrombopoiesis in patients with low platelet counts. This approach has clearly been effective for targeted treatment of anaemia and neutropenia using recombinant erythropoietin (epoetin alpha, darbepoetin alpha and epoetin beta) and granulocyte colony-stimulating factor (filgrastim and pegfilgrastim).[46–48] Several recent studies have confirmed the importance of TPO in patients with chronic liver disease including studies showing that liver fibrosis (grade 3/4) and liver function correlate with low TPO serum levels.[15, 49] As TPO is synthesized in the liver, impaired hepatic function may reduce TPO production.[3, 50]

Table 1. Ideal therapy for thrombocytopenia in liver disease

Optimal therapy for thrombocytopenia should be:
Effective in the majority of treated patients
Orally bioavailable
Active across various disease states
Relatively free of adverse effects
Cost-effective

The cloning of human TPO, and the identification and development of the related compound, recombinant human megakaryocyte growth and development factor (rHuMGDF), allowed for clinical evaluation of these agents in patients with thrombocytopenia. Both TPO and rHuMGDF were shown to increase median platelet counts and reduce the magnitude of the platelet count nadir when given before and after chemotherapy.[36] Clinical development of TPO and rHuMGDF was halted due to the development of neutralizing antibodies in some patients, which caused the inactivation of endogenous TPO. Other agents including cytokines such as interleukin-11 (IL-11), synthetic TPO ligands and mimetics (AMG 531, Peg-TPOmp, AKR-501) and platelet-targeted growth factors like eltrombopag are under development (Table 2).[51–55] IL-11, while approved for the treatment of chemotherapy-induced thrombocytopenia, can be associated with significant toxicity including leg oedema and pulmonary congestion.[53, 55] A number of second-generation non-peptide compounds such as eltrombopag and AKR-501 have shown significant dose-dependent increases in platelet counts and an acceptable toxicity profile.[53, 54] A detailed

Table 2. Novel therapies for thrombocytopenia

Recombinant human thrombopoietin (rHuTPO)
Recombinant human megakaryocyte growth and development factor (rHuMGDF)
TPO non-peptide mimetics (eltrombopag, AKR-501)
Recombinant interleukin-11 (rHuIL-11)
Thrombopoietin mimetics (AMG-531, Peg-TPOmp)

review of platelet-targeted compounds and their mechanisms of action is presented in an accompanying article by Drs McHutchison and Afdhal.

COST OF THROMBOCYTOPENIA

For patients with chronic liver disease, thrombocytopenia can increase treatment costs in many ways. Some factors to consider are the cost of therapy to correct platelet counts [including platelet transfusions and/or treatments for refractory patients (splenic artery embolization, splenectomy)], missed or delayed procedures, laboratory work and increased hospitalization and staff charges. Transfusion-related complications could require additional therapy and incur additional costs.[56]

In 1998, total direct healthcare costs associated with HCV were estimated at more than $1 billion in the United States.[57] Because effective HCV treatment is cost-effective based on gains in health-related quality of life (QOL) and overall cost savings,[58] the ability to initiate and complete IFN-based anti-viral therapy could significantly reduce overall healthcare costs.

Approaches that could increase platelet counts without the risks associated with platelet transfusions could lower healthcare costs for patients with chronic liver disease by decreasing hospitalization costs, avoiding delays in required diagnostic or invasive procedures, and raising QOL. A detailed discussion of the cost of thrombocytopenia for care of patients with chronic liver disease, including pharmacoeconomic analyses, is presented by Dr Robert Brown Jr, in an accompanying article in this supplement.

CONCLUSIONS

Better therapeutic options are needed to safely and effectively increase platelet counts, especially for patients with chronic liver disease. Novel agents that function as platelet growth factors targeting TPO receptor-mediated pathways show promise in treating thrombocytopenia.[59] Given the potential number of procedures and therapies that are postponed or cancelled because of thrombocytopenia and the risk of bleeding complications, many chronic liver disease patients could likely benefit from interventions that would increase platelet counts to >100 000/μL. Treatments administered preoperatively to increase platelet counts and reduce the need for platelet transfusions would allow for planned diagnostic or therapeutic procedures and facilitate initiation and/or maintenance of planned anti-viral therapy in patients with chronic liver disease. The continuing clinical development of non-peptide and non-immunogenic peptide TPO mimetics including eltrombopag and AMG 531 may fulfil many of these criteria, with a significant impact on thrombocytopenia in patients with liver disease.

Finally, standardized evidence-based guidelines for transfusion support in thrombocytopenic patients with chronic liver disease during invasive procedures including liver biopsy, endoscopy and dental extractions might be useful to the clinician. Clinicians need better information on the risk of bleeding complications according to the degree of thrombocytopenia and other coagulopathies. Providing clinicians with additional guidelines specific for this patient population may lead to cost savings and improved patient management.

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