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Quarterly Review

Chronic hepatitis C-associated thrombocytopenia: aetiology and management

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ABSTRACT

Thrombocytopenia is perhaps the most common haematological abnormality in patients with chronic hepatitis C virus (HCV) infection. In these patients, the presence of thrombocytopenia may be a limiting factor when considering antiviral therapy and may be associated with decreased sustained virological response rates. Thrombocytopenia may interfere with diagnostic procedures such as liver biopsy, because of risk of bleeding. Pathogenetic mechanisms include hypersplenism secondary to portal hypertension, bone marrow suppression resulting from either HCV itself or interferon treatment, and aberrations of the immune system resulting in the formation of anti-platelet antibodies and/or immune-complexes that bind to platelets and facilitate their premature clearance. The ability to increase platelet levels could significantly reduce the need for platelet transfusions and facilitate the use of interferon-based antiviral therapy and other medically indicated treatments in patients with liver disease. Therapeutic options include pharmacological and non-pharmacological therapies. This review summarizes the available data on these therapeutic options.

KEYWORDS: thrombocytopenia, hepatitis C virus (HCV), cytokines

Definition and prevalence

Thrombocytopenia has been defined as a platelet count <150,000 cells/μL. In a recent systematic review, the definitions of thrombocytopenia varied between studies and were based either on platelet counts, with threshold levels ranging between ≤100,000 cells/μL and ≤180,000 cells/μL or on criteria set in haematological guidelines.[1]

The prevalence of thrombocytopenia related to chronic liver disease has been reported as 15% to 70% in patients with advanced fibrosis and portal hypertension, depending on the stage of the disease and the platelet level used to define thrombocytopenia.[2–4] Patients with more advanced end-stage disease tend to have a higher degree of thrombocytopenia than those with compensated liver disease.[5] Approximately 25% to 50% of cirrhotic patients have counts of <100,000 cells/μL.[2,6] Platelet counts of <50,000 cells/μL occur in approximately 1% of patients with chronic HCV infection.[2]

In patients with chronic HCV infection, the prevalence of thrombocytopenia ranged from 0.16% to 45.4% and more than half of the studies reported a prevalence of 24% or more.[1]

Aetiology of thrombocytopenia in patients with chronic HCV

The pathophysiology of thrombocytopenia in patients with HCV-related chronic liver disease is complex and involves the interaction of multiple factors. In general, these factors may be

grouped into disease-related factors and treatment-related factors. Factors related to the disease include hepatic fibrosis or cirrhosis, hypersplenism, bone marrow suppression, immune dysfunction and decreased thrombopoietin levels or activity.

Hepatic fibrosis

The prevalence and severity of thrombocytopenia is associated with the severity of hepatocellular damage, as shown by an increased degree of fibrosis. The inverse correlation between platelet count and severity of hepatic fibrosis was shown in treatment-naive patients with chronic HCV infection.[7]

Hypersplenism

Several studies have shown an inverse correlation between spleen size and platelet count in patients with chronic HCV infection.[8–10] Redistribution of blood to the spleen due to portal hypertension results in pooling of platelets in the spleen and increased clearance of platelets from the circulation.[11] Splenomegaly and platelet sequestration, or hypersplenism, is observed in 11%–55% of patients with cirrhosis and portal hypertension[3,12] and, therefore, does not explain all cases of thrombocytopenia in chronic HCV infection.[13,14]

Bone marrow suppression

Bone marrow suppression caused by HCV infection has been proposed as a contributing factor in the development of thrombocytopenia.[15] In some patients, the reduction of HCV RNA levels following interferon treatment correlated with significant increases in platelet counts in the absence of hypersplenism or serological evidence of platelet autoantibodies.[13] Excessive consumption of alcohol may have additional direct toxic effects on megakaryocytes resulting in decreased platelet production and ineffective thrombopoiesis.[16]

Immune dysfunction

In patients with chronic HCV infection, autoantibodies directed against platelet surface antigens can promote platelet sequestration and destruction by fixed macrophages in the spleen and liver.[8,17,18] It has been suggested that the binding of HCV to platelets may induce the development of neoantigens on the platelet surface or alter the conformation of platelet membrane glycoproteins (GPs), thereby contributing to autoantibody formation against target platelet GPs.[19] Immune complex-associated platelet clearance and reticulo-endothelial destruction have been proposed to contribute to thrombocytopenia in patients with chronic HCV infection.[18] High titres of platelet-associated immunoglobulin G (PAIgG), which could represent immune complex-coated platelets, have been found in up to 88% of patients with chronic HCV infection.[8,20,21] The PAIgG levels have been shown to correlate directly with severity of liver disease,[21] suggesting that prolonged HCV infection causes marked abnormalities of the immune system.

Decreased thrombopoietin levels or activity

Thrombopoietin, also known as c-Mpl ligand, is the prime cytokine implicated in megakaryocyte maturation and platelet production. It is produced mainly by hepatocytes and usually released into the circulation at a constant rate.[22] Thrombopoietin binds to c-Mpl receptors on haematopoietic stem cells and megakaryocytes and promotes all stages of platelet production, from megakaryocyte proliferation to maturation and platelet formation. At various stages of platelet production, circulating thrombopoietin acts in conjunction with other haematopoietic cytokines, including interleukin (IL)-11, steel factor, erythropoietin, and stromal cell-derived factor-1.[23,24] Thrombopoietin also binds to platelets and enhances platelet activation and function.[23] Platelets not only bind to thrombopoietin but also internalize and degrade it.[22] As a result, serum levels of thrombopoietin are normally regulated by the total platelet mass, including platelets sequestered in the spleen, rather than by its production rate.[23] Under normal conditions, if platelet production decreases, the circulating platelet count falls, less thrombopoietin binds to platelets, and as a result, the plasma thrombopoietin concentration increases. Consequently, megakaryocytopoiesis increases to restore platelet homeostasis, resulting in more production and release of platelets. When the platelet count increases, excess thrombopoietin is bound by circulating platelets, and thrombopoietin levels decrease to normal levels.

It is important to understand that serum thrombopoietin levels in patients with chronic liver disease do not reflect thrombopoietin production alone but also the complex interactions between thrombopoietin production, thrombopoietin degradation, platelet turnover and thrombocytopenia. In patients with chronic liver disease, serum

thrombopoietin levels have been reported to be low, normal or elevated in the presence of thrombocytopenia.[10,12]

Treatment-related thrombocytopenia

Thrombocytopenia is a well-known adverse effect of peginterferon, which, together with ribavirin, is the current treatment of choice for chronic HCV infection. Interferon (IFN) therapy is known to cause a 10%–50% fall in the platelet count. It is more severe with pegylated interferon/ribavirin (PEG-IFN/RBV) combination therapy as compared to non-pegylated IFN/RBV therapy. It is worst with PEG-IFN monotherapy,[25-6] suggesting that some reactive thrombocytosis may be occurring secondary to RBV-induced anaemia. Moreover, successful treatment of HCV infection has clearly shown to improve the platelet counts.[27,28]

Bone marrow suppression, including inhibition of megakaryocytopoiesis, is considered to be the major mechanism of interferon-induced thrombocytopenia.[29] There is also evidence that interferon treatment may suppress the secretion of thrombopoietin.[30]

The most important clinical consequence of thrombocytopenia during interferon-based therapy is that it can result in reduction of total doses of interferon, resulting in suboptimal therapy and lowered opportunity for the patient to achieve sustained virological response.

Impact of thrombocytopenia on the management of HCV infection

The greatest challenge in the care of chronic HCV patients with thrombocytopenia is the difficulty in initiating or maintaining anti-HCV therapy. In general, initiation of antiviral therapy is contraindicated when platelet counts are below 75,000–100,000 cells/μL. The American Gastroenterological Association suggests that patients with severe thrombocytopenia should not receive interferon-based antiviral therapy.[31] Postponement of treatment due to thrombocytopenia can result in diminished sustained virological response because of the potential for further progression of liver disease in the absence of treatment; it may also heighten the need for additional therapies.[32]

The product labels for both the formulations of peginterferon recommend dose reductions for patients with platelet counts between 50,000 and 80,000 cells/μL and discontinuation of therapy if platelet counts falls below 25,000–50,000 cells/μL.[31] Treatment with peginterferon has been shown to reduce platelet counts by up to 33%.[33] Therefore, even in patients with adequate platelet counts before therapy, platelet counts may decreases during therapy, which could require a dose modification that may ultimately lower the chances of attaining sustained virological response.

An important clinical concern with thrombocytopenia is the inability to initiate or maintain therapeutic or diagnostic interventions, which arises from the likelihood that low platelet counts may lead to increased morbidity or mortality. Thrombocytopenia can complicate or delay certain aspects of routine care due to the increased risk of bleeding from invasive procedures. These procedures include liver biopsies by any route,[34–36] variceal banding, paracentesis[37–39] and thoracentesis , liver transplantation,[39] central line insertion, endoscopy, prostate biopsy and elective surgeries. Some physicians avoid or postpone these procedures, as well as dental extractions, because of concerns about haemorrhage.[2,34] This trepidation can cause postponement of necessary procedures and therapy, hinder planned medical care, and significantly add to healthcare costs in these patients.

Strategies for the management of thrombocytopenia in patients with chronic HCV infection

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.[40,41] The minimum effective dose of PEG-IFN 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.[42]

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 elevation in serum

bilirubin levels and development of overt jaundice.[43]

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.[44,45] 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.[45] Refractoriness typically arises from human leukocyte antigen alloimmunization and non-immune platelet consumption associated with splenomegaly, disseminated intravascular coagulation and septicaemia.[45]

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.[45] For patients with platelet counts <20,000 cells/μL, platelet transfusions are given or the planned medical procedure is postponed.[46] Patient populations at higher risk for bleeding complications, including surgical patients and those with infection or splenomegaly, may warrant higher cut-off values of 50,000–100,000 cells/μL.[47] 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,[48] 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.[23,48]

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.[49,50] 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 findings led to the discontinuation of research on possible therapeutic uses of these cytokines for the treatment of thrombocytopenia.[51]

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.[52] However, in a phase 1 clinical study, antibody formation resulted in severe thrombocytopenia, terminating further development of promegapoietin.[53]

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.[54] 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.[54] However, oprelvekin is not currently approved for chronic liver disease-related thrombocytopenia.

Targeting thrombopoietin receptor activation: thrombopoietin agonists

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.[54,55]

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.[56] The study enrolled 74 patients with evidence of liver damage, which was characterized by a liver biopsy indicating chronic hepatitis and cirrhosis or radiographic evidence of cirrhosis or non-bleeding gastroesophageal varices and compensated liver disease (Child–Pugh A). Inclusion criteria included presence of thrombocytopenia at platelet counts of 20,000–70,000 cells/μL, whereas patients were excluded for a history of thrombosis, HIV infection, or active hepatitis B virus infection. Patients received 30, 50 or 75 mg/day eltrombopag or placebo daily for 4 weeks. After 4 weeks, patients were evaluated before initiation of the antiviral treatment phase of the trial. 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).[57]

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.[58,59] 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.[60] 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.[61]

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) immuneglobulin, anti-D therapy). Safety data from these studies indicate that romiplostim is well tolerated, with no serious adverse events.[60,61]

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.[62] The administration of such minibodies to cynomolgus monkeys increased platelet counts.[62]

Danazol

Danazol therapy was useful and well tolerated when used for treatment of refractory autoimmune thrombocytopenia with unknown mechanism.[63,64] It has been shown that danazol therapy modifies the level of antiplatelet antibodies and inhibits the mononuclear phagocyte system in patients with refractory thrombocytopenia.[65,66] 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.[67] 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.[68–73] In a recent study, L-carnitine added to Peg-IFN-α plus ribavirin led to less decrease of platelet count during antiviral therapy.[74] Some studies indicate that L-carnitine modulates platelet functions and production through antioxidant mechanisms and the inhibition of the arachidonic acid cascade.[75–78] 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.[78]

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.[79,80] 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 re-exploration have been described as complications.[81,82] 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 parenchyma. 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.[83–86]

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.[87] 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.[88]

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.[89,90]

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.[91,92] 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.[93]

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 thrombopoietin-mimetic 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-associated thrombocytopenia. PSE represent a safe and effective non-pharmacological treatment option replacing splenectomy for thrombocytopenia.

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