Thrombocytopenia in Patients with Chronic Hepatitis C Virus Infection

Sumit Dahal,1 Smrity Upadhyay,2 Rashmi Banjade,3 Prajwal Dhakal,4 Nabin Khanal2 and Vijaya Raj Bhatt5

1 Interfaith Hospital, Department of Medicine, New York, USA.
2 Creighton University Medical Center, Department of Internal Medicine, Omaha, Nebraska, USA.
3 Montefiore New Rochelle Hospital, Department of Medicine, New York, USA.
4 Michigan State University, Department of Medicine, East Lansing, Michigan, USA.
5 University of Nebraska Medical Center, Department of Internal Medicine, Division of Hematology-Oncology, Omaha, Nebraska, USA.

Competing interests: The authors have declared that no competing interests exist.

Abstract. Thrombocytopenia in patients with chronic hepatitis C virus (HCV) infection is a major problem. The pathophysiology is multifactorial, with auto-immunogenicity, direct bone marrow suppression, hypersplenism, decreased production of thrombopoietin and therapeutic adverse effect all contributing to thrombocytopenia in different measures. The greatest challenge in the care of chronic HCV patients with thrombocytopenia is the difficulty in initiating or maintaining IFN containing anti-viral therapy. Although at present, it is possible to avoid this challenge with the use of the sole Direct Antiviral Agents (DAAs) as the primary treatment modality, thrombocytopenia remains of particular interest, especially in cases of advanced liver disease. The increased risk of bleeding with thrombocytopenia may also impede the initiation and maintenance of different invasive diagnostic and therapeutic procedures. While eradication of HCV infection itself is the most practical strategy for the remission of thrombocytopenia, various pharmacological and non-pharmacological therapeutic options, which vary in their effectiveness and adverse effect profiles, are available. Sustained increase in platelet count is seen with splenectomy and splenic artery embolization, in contrast to only transient rise with platelet transfusion. However, their routine use is limited by complications. Different thrombopoietin analogues have been tried. The use of synthetic thrombopoietins, such as recombinant human TPO and pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMDGF), has been hampered by the development of neutralizing antibodies. Thrombopoietin-mimetic agents, in particular, eltrombopag and romiplostim, have been shown to be safe and effective for HCV-related thrombocytopenia in various studies, and they increase platelet count without eliciting any immunogenicity. Other treatment modalities including newer TPO analogues- AMG-51, PEG-TPOmp and AKR-501, recombinant human IL-11 (rhIL-11, Oprelvekin), recombinant human erythropoietin (rhEPO), danazol and L-carnitine have shown promising early result with improving thrombocytopenia. Thrombocytopenia in chronic HCV infection remain a major problem, however the recent change in DAAs without IFN, as the frontline therapy for HCV, permit to avoid the dilemmas associated with initiating or maintaining IFN based anti-viral therapy.

Keywords: Hepatitis C, Chronic; Hepatitis C, Chronic/ complications; Hepatitis C, Chronic/ drug therapy; Thrombocytopenia/virology; Thrombocytopenia/drug therapy; Direct-acting antivirals/therapeutic use; Ribavirin/therapeutic use; Interferon-alpha/ therapeutic use.

Citation: Dahal S., Upadhyay S., Banjade R., Dhakal P., Khanal N., Bhatt V.R. Thrombocytopenia in patients with chronic hepatitis c virus infection. Mediterr J Hematol Infect Dis 2017, 9(1): e2017019, DOI: http://dx.doi.org/10.4084/MJHID.2017.019

Published: March 1, 2017 Received: November 21, 2016 Accepted: February 7, 2017

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Introduction. Chronic hepatitis C virus (HCV) infection affects 3% of the world’s population and 1.3% of the United States’ population.\textsuperscript{1,2} It is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma, and is one of the most common causes of liver transplants in the United States.\textsuperscript{2} Besides hepatic complications, chronic HCV infection is also associated with several extra-hepatic manifestations including thrombocytopenia. Thrombocytopenia in chronic HCV infection is a major problem, particularly in patients with advanced liver disease. The risk of serious bleeding with severe thrombocytopenia can prevent invasive procedures including biopsies for staging.\textsuperscript{3} Thrombocytopenia can also complicate bleeding manifestations such as variceal bleeding. It may impede the initiation and continuation of antiviral therapy, potentially decreasing the probability of successful HCV treatment.\textsuperscript{4} Recent studies have evaluated the underlying mechanism of thrombocytopenia in chronic HCV infection and assessed the usefulness of several therapeutic options.

Epidemiology. The prevalence and degree of thrombocytopenia increase with the severity of liver disease and correlates to hepatocellular damage and hepatic fibrosis.\textsuperscript{5} However, use of varying definition for thrombocytopenia and insufficient data on study characteristics such as age, gender, HCV treatment rates and disease severity preclude a more accurate estimate of the overall prevalence.\textsuperscript{6} A systematic review estimated the average prevalence of thrombocytopenia in chronic HCV infection to be nearly 24% (Table 1).\textsuperscript{6}

Table 1. Prevalence of thrombocytopenia in chronic hepatitis C infection.

| Author              | Study Design | Total cases in study | Platelet counts (X 10\(^6\)) | Cases with cirrhosis (%) | Cases receiving Anti-viral therapy (%) | Cases with thrombocytopenia (%) |
|---------------------|--------------|----------------------|-------------------------------|--------------------------|--------------------------------------|-------------------------------|
| Ikeda et. al[70]    | Cohort       | 1056                 | 140-150                       | 9.7                      | 8.2                                  | 38.7                          |
| Moriyama et. al [71]| Cohort       | 645                  | 140-150                       | NR                       | 0.0                                  | 29.2                          |
| Nagamine et. al [72]| Cross-sectional | 368                 | 140-150                       | 0.0                      | NR                                   | 41.0                          |
| Ordi-Ros et al. [73]| Cross-sectional | 230                 | 140-150                       | 11                       | 8.3                                  | 18.3                          |
| Poynard et al. [74] | Cross-sectional | 1354                | 140-150                       | NR                       | 0.0                                  | 31.1                          |
| Sylvestre et al. [75]| Cross-sectional | 409                 | 140-150                       | NR                       | NR                                   | 31.1                          |
| Shanmuganathan et al.[76]| Cross-sectional | 182                 | 140-150                       | 9.9                      | NR                                   | 28.0                          |
| Taliani et al. [77] | Cross-sectional | 78                  | 140-150                       | 48.7                     | 0.0                                  | 44.8                          |
| Borroni et. al. [78] | Cross-sectional | 228                 | 130-140                       | 13.2                     | 0.0                                  | 9.6                           |
| Dalekos et al. [79] | Cohort       | 75                   | 130-140                       | NR                       | NR                                   | 13.3                          |
| Kaul et al. [80]    | Cross- sectional | 264                 | 130-140                       | 3.3                      | Nr                                   | 28                            |
| Luo et al. [81]     | Cross- sectional | 111                 | 130-140                       | 20.7                     | NR                                   | 28.9                          |
| Prieto et al. [82]  | Cross-sectional | 100                 | 130-140                       | 25                       | 16                                   | 45                            |
| Romagnuolo et al. [83]| Cross-sectional | 54                  | 130-140                       | 7.4                      | 0.0                                  | 24.1                          |
| Zachou et. al. [84] | Cohort       | 174                  | 130-140                       | 20.7                     | 30.0                                 | 31.2                          |
| Hu et. al. [85]     | Cohort       | 112                  | 100-130                       | 100                      | 43.8                                 | 30.3                          |
| Kim et al. [86]     | Cross Sectional | 141                | 100-130                       | 7.4                      | NR                                   | 24.8                          |
| Renou et al. [87]   | Cross Sectional | 110                | 100-130                       | 12.7                     | 0.0                                  | 18.2                          |
| Cicardi et al. [88] | Cohort       | 360                  | <100                          | 24                       | 0.0                                  | 16.4                          |
| Nahon et al. [89]   | Cohort       | 97                   | <100                          | 100                      | NR                                   | 45.4                          |
| Wang et al. [90]    | Cross Sectional | 140                | <100                          | 5.0                      | NR                                   | 15.7                          |
Mechanism. The pathophysiology of thrombocytopenia in patients with HCV infection is thought to be multifactorial. Besides inducing an autoimmune reaction with production of anti-platelet antibodies, the virus also causes direct bone marrow suppression with resulting thrombocytopenia.\textsuperscript{7-10} Chronic HCV infection induced liver fibrosis and cirrhosis leads to portal hypertension with subsequent hypersplenism and sequestration of platelets, decreased the production of thrombopoietin, and endothelial dysfunction, all of which can contribute to thrombocytopenia.\textsuperscript{11-14} Although uncommonly used in developed countries, interferon (IFN) and ribavirin used as part of anti-HCV therapy can also contribute to low platelet count.\textsuperscript{15}

Impact on Clinical Management. Although thrombocytopenia in chronic HCV infection is typically low grade and not life-threatening, it represents an obstacle to different diagnostic or therapeutic modalities and may preclude the use of anti-viral treatment.

The greatest challenge in the care of chronic HCV patients with thrombocytopenia is the difficulty in initiating or maintaining IFN containing anti-viral therapy. Although this challenge can be avoided with the use of sole DAAs as the primary treatment modality, thrombocytopenia remains of particular interest, especially in cases of advanced liver disease. In a study by Wang et al., baseline thrombocytopenia increased the risk of drug cessation. Patients with baseline thrombocytopenia actually exhibited compromised sustained virelogic response (SVR) rates while those with acquired thrombocytopenia did not. Thus, use of growth factors to maintain SVR rate would be beneficial in those with baseline thrombocytopenia rather than in those who acquire it during therapy as dose reduction doesn’t decrease SVR in such cases.\textsuperscript{16}

Thrombocytopenia in HCV may also be a problem for patients with baseline platelet count of <50,000/mm\textsuperscript{3}, particularly in the presence of previous bleeding even when they are treated with DAAs. However, patients with thrombocytopenia and fibrosis have attained >90% SVR with DAAs even if in a proportion lower in respect to patients with a normal platelet count. Thus, DAAs may be continued most of the times without interruption and thrombopoietin mimetics would be helpful only with severe thrombocytopenia (such as a platelet count of <25,000/mm\textsuperscript{3}).\textsuperscript{17-19}

Directly-acting antivirals (DAAs): Recently updated World Health Organization guidelines recommend that DAA regimens (including simeprevir, grazoprevir, daclatasvir, ledipasvir, and sofosbuvir) be used for the treatment of persons with hepatitis C infection rather than regimens with pegylated interferon and ribavirin.\textsuperscript{16} Combinations of 2 or 3 DAAs have been shown to be highly effective and safe in both cirrhotic and non-cirrhotic patients in different phase III clinical trials and large real life cohorts with providing SVR rates of >95%. While headache, diarrhea, fatigue, and nausea have frequently been observed, hematologic abnormalities including thrombocytopenia were reported in no more than 1% of cases.\textsuperscript{17,18} Lee et al. reported that DAA therapy in one patient precipitated ITP refractory to various treatment modalities and it required several weeks of therapy with multiple platelet transfusions, intravenous immunoglobulin, steroids and romiplostim to achieve a stable platelet count of 40,000/mm\textsuperscript{3} with no signs of bleeding.\textsuperscript{19} However, this is only one case describing any relation of DAA with thrombocytopenia. A study by Forns et al. showed that HCV genotype 1a-infected patients with surrogate markers of portal hypertension or impaired liver function such as thrombocytopenia and hypoalbuminemia at baseline achieved high SVR rates with ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin and treatment was well tolerated.\textsuperscript{20} Additionally, reduction in liver fibrosis markers such as fibrosis-4 score and aspartate transaminase platelet ratio along with regression of transient elastography have been reported with use of DAAs in chronic hepatitis C.\textsuperscript{21} In any case, by the time, thrombocytopenia improves following SVR obtained with any antiviral therapy among chronic HCV infected patients with advanced hepatic fibrosis.\textsuperscript{21,22}

INF based antiviral therapy: Although IFN based antiviral therapy is uncommonly used in developed countries nowadays, the prohibitive cost of DAA may require the use of INF based therapy along with the addition of thrombopoietin mimetics, if required, in economically disadvantaged areas. Additionally, in chronic hepatitis C cases treated with pegylated INF plus
ribavirin, single nucleotide polymorphisms at or near the IL-28B gene have been shown to be a predictor of SVR. The American Gastroenterological Association recommends dose reduction of INF with a platelet count between 25,000-50,000 and withdrawal of INF-based treatment with a count below 25,000. This is important because the antiviral therapy itself may cause a further drop in platelet count. Studies have shown IFN-based therapy to cause severe thrombocytopenia in up to 13% of patients, with the incidence higher in patients with lower baseline platelet count. The modifications in IFN-based therapy have potential to lower the chances of attaining SVR. The increased risk of bleeding may also impede the initiation and maintenance of different invasive diagnostic and therapeutic procedures such as liver biopsy, variceal banding, paracentesis and thoracentesis, central line insertion, endoscopy and elective surgery.

**Management.** Various pharmacological and non-pharmacological therapeutic options are available for the management of thrombocytopenia in chronic HCV infection (Table 2). These treatment modalities vary in their effectiveness and adverse effect profiles. The most practical strategy in treating HCV-related thrombocytopenia is based on the principle that eradication of HCV infection may result in remission of thrombocytopenia. By eradicating HC virus, DAAs are supposed to improve thrombocytopenia related to hepatitis C infection but may not ameliorate thrombocytopenia related to cirrhosis or portal hypertension. In cases of IFN based antiviral therapy, the usual approach is to continue with the therapy, reducing the dose if platelet count drops below 50,000 cells/μL or discontinuing it for a platelet count of below 25,000 cells/μL. The measures described below are mostly supportive. As expected, there is a lot of published data on how these measures might be necessary to IFN-based therapy but not to them with DAAs.

**Platelet transfusion:** Though widely used for the management of thrombocytopenia, platelet transfusion has several limitations, especially in patients with chronic liver disease. The increase in platelet count is transient, and hence useful only for procedures or during bleeding. Patients are also at risk for transfusion-related complications, which can occur in up to 30% of the recipients and include viral or bacterial infection, febrile non-hemolytic reactions, and iron overload. Nearly half of all patients undergoing multiple platelet transfusions can develop platelet refractoriness secondary to human leukocyte antigen (HLA) alloimmunization. It may not always ensure maintenance of homeostatic platelet levels. Besides, the requirement of hospitalization and high cost may be prohibitive in a resource-poor setting.

**Splenectomy and splenic artery embolization:** Splenectomy and splenic artery embolization have been used to correct thrombocytopenia in patients with hypersplenism, producing significant and persistent increases in platelet count. Akahoshi et al. studied the effect of splenectomy in patients with HCV-associated thrombocytopenia and found above 200% rise in mean platelet count at 1 month after splenectomy. In cases of IFN-based antiviral therapy, the positive effect is known to persist even after the initiation of antiviral therapy, with the mean platelet count nearly 80% above baseline after 12 months of the therapy. Splenectomy, however, is an invasive procedure with high risk of bleeding, sepsis and portal vein thrombosis. Asplenic patients are susceptible to overwhelming post-splenectomy infection. Splenic artery embolization may be an alternative option. In a study by Barcena et al., the mean platelet count increased by 342% from the baseline after 12 weeks of partial splenic artery embolization. Splenic artery embolization, though associated with lower morbidity and mortality than splenectomy, is not free of complications.

**Pharmacotherapy:** **Steroids:** With HCV reported to play a pathogenic role in some cases of immune thrombocytopenic purpura, there have been case reports of significant improvement in HCV-related thrombocytopenia with the use of corticosteroid. As described earlier, Lee et al. described a case of resistant ITP which developed after DAA therapy and did not respond to high dose prednisone. Lebano et al. reported a case where the platelet count increased by 175% from baseline six months after steroid therapy and improved further (360% above baseline) after another six months of IFN and ribavirin. Despite similar reports of steroids causing a variable rise in platelet counts, they are not routinely considered in the management of
thrombocytopenia in HCV infection because of the possible risk of worsening viral loads and liver damage.38,39

**Thrombopoietin analogue:** Thrombopoietin (TPO) is a cytokine predominantly synthesized by the hepatocytes in the liver and plays a central role in thrombopoiesis. It binds to TPO receptors (mpl) expressed on the surface of megakaryocyte precursor cells and megakaryocytes, activating signal transduction cascades that result in proliferation and maturation of megakaryocytes.40

A better understanding of TPO and its role in platelet production and function has led to newer treatment modalities. Synthetic thrombopoietins such as recombinant human TPO and pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMDGF) cause an increase in platelet count.41,42 However, their use has been hampered by the appearance of neutralizing antibodies that cross-reacts with both recombinant and endogenous TPO.43 In a study using PEG-rHuMDGF injection by Li et al., an initial rise in platelet count was followed by the development of an antibody against TPO, detected as early as 56 days after the initial injection.44 This was associated with corresponding fall in platelet count and a marked decrease in bone marrow megakaryocytes, with an average nadir platelet count of 6% to 8% of baseline.

Thrombopoietin-mimetic agents, in particular, eltrombopag and romiplostim, have been shown to increase platelet count without eliciting any immunogenicity.45-47 Romiplostin is a peptibody composed of four TPO mimetic peptides attached by glycine bridges to the heavy chain portion of immunoglobulin G. It acts by dimerizing the TPO receptor via its paired peptides, which stimulates platelet production.48 It is given by weekly subcutaneous injections. Various clinical trials in patients with chronic immune thrombocytopenic purpura have shown romiplostin to cause a dose dependent increase in platelet count, resulting in lower rates of treatment failure, decreased the need for splenectomy and improved quality of life.49-51 Lee et al. described romiplostim use in a case of resistant ITP after DAA therapy.52 A study by Moussa et al. in 35 patients with chronic liver disease and thrombocytopenia secondary to HCV infection found that romiplostin to cause a dose dependent increase in platelet count, with an average nadir platelet count of 6% to 8% of baseline.53

### Table 2. Management of hepatitis C-related thrombocytopenia.

| Author/Study | Year | No. of patients | Baseline platelet, mean or median (range) | Intervention | Mean/median platelet count after the intervention | Major complications |
|-------------|------|----------------|------------------------------------------|-------------|-----------------------------------------------|---------------------|
| Akahoshi et al. [35] | 2011 | 100 | 56,000 (22,000 – 75,000) | Splenectomy followed by PEG-IFN+RBV | 105,000 (range 40,000 – 140,000) at 6 months | Portal vein thrombosis (7%), Wound infection (4%), Bleeding (2%) |
| Barcena et al. [36] | 2005 | 3 | 44,067 (39,900 – 50,300) | Partial splenic artery embolization | 195,000 (128,000 – 243,000) at 12 months | |
| Afdhal et al. ENABLE-1 [57] | 2014 | 715 | 59,000 | PEG-IFN2a / Ribavirin plus Eltrombopag vs. placebo | Median increase of 31,000 or 54,000 (depending on the dose of Eltrombopag) vs. Median decrease of 25,000 | Thrombo-embolic events (3% vs 1%); Hepatic decompensation (10% vs 5%) |
| Afdhal et al. ENABLE-2 [57] | 2014 | 805 | 59,000 | PEG-IFN2b / Ribavirin plus Eltrombopag vs. placebo | 105,000 vs. 55,000 at 45 weeks | Thrombo-embolic events (4% vs 0.4% ); Hepatic decompensation (10 vs 5%) |
| Moussa et al. [52] | 2012 | 35 | 31,000 (21,000–46,000) | Romiplostim | 46,000 (range 26,000 – 88,000) at 3 months (2 months after stopping treatment) | Anemia (40%), Headache (38%), Arthralgia (31%), Myalgia (31%), Malaise (29%), Nausea (26%), Hypothenia (24%) |
| Alvarez et al. [91] | 2011 | 49 | 69,067 (34,000 – 88,200) | Danazol plus IFN plus Ribavirin | 121,081 (range 46,000 – 216,000) | |
| Malaguarnera et al. [92] | 2011 | 69 | 384,000 vs. 412,000 | PEG-IFN + RBV with or without L-carnitine | 298,000 vs. 327,000 at 12 months | |
| Lawitz et al. [65] | 2004 | 20 | 143,000 (43,000 – 244,000) | Recombinant human IL-11 (Oprelvekin) | Median of 198,000 at 45 weeks | Edema of lower extremities (100%) |
infection showed more than three-fold increase in mean platelet count from the baseline after 3 weeks of therapy. And the mean platelet count remained 1.5 times above the baseline even after 2 months of stopping the drug. Similarly, Voican et al. reported two cases where romiplostin was used to control severe thrombocytopenia; this allowed anti-HCV treatment with pegylated-IFN and ribavirin to be completed successfully without any dose reduction or discontinuation.

Eltrombopag, an orally active TPO agonist, interacts with the trans-membrane domain of the thrombopoietin receptor, activating JAK2/STAT signaling pathways and increasing proliferation and differentiation of human bone marrow progenitor cells into megakaryocytes. Preclinical studies have shown the binding site on the receptor and the signal transduction mechanism to be different for eltrombopag as compared to thrombopoietin, causing the two to have an additive effect on platelet production. Eltrombopag has been found to be safe and effective in the management of HCV-related thrombocytopenia. In a phase II trial, 71-91% of the patients receiving eltrombopag had a dose dependent increase in their platelet counts to levels which allowed initiation of antiviral therapy. 36-65% of patients in the eltrombopag group completed first 12 weeks of antiviral therapy compared to 6% in the placebo group. Though platelet counts decreased during the antiviral treatment phase despite the use of eltrombopag, the count consistently remained above baseline as well as above the level at which a reduction in the pegylated-IFN dose is recommended (<50,000 per cubic millimeter). Another phase III trial, Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C-Related Liver Disease (ENABLE-1 and ENABLE-2), showed a higher rate of sustained virological response with the use of eltrombopag than placebo (23% vs. 14%, p = 0.0064 in ENABLE-1 and 19% vs. 13%, p = 0.0202 in ENABLE-2). Pegylated-IFN was administered at higher doses, with fewer dose reductions in the eltrombopag group. Throughout the antiviral treatment, a platelet count of 50,0000 per cubic millimeter or higher was maintained in more patients receiving eltrombopag than placebo (69% vs. 15% in ENABLE-1 and 81% vs. 23% in ENABLE-2).

The most common side effect with these thrombopoietin-mimetic agents is a headache, with the reported incidence in clinical trials ranging from 7% to 21%. Eltrombopag also commonly causes dry mouth, abdominal pain, and nausea, and may be associated with hepatic decompensation like ascites and hepatic encephalopathy. Romiplostin may be associated with increased deposition of reticulin in the bone marrow, and possibly narrow fibrosis. The risk of thromboembolic events like portal vein thrombosis is seen with all these agents.

Other newer drugs currently under investigation include the peptidic compounds like AMG-531 and PEG-TPOmp, non-peptidic compound like AKR-501, and monoclonal antibodies. AMG-531, a TPO agonist, has been designed with no sequence homology to human TPO to reduce the likelihood of an anti-TPO immune response. Phase II and III studies in ITP patients have shown promising early results with a dose-dependent increase in platelet count with no serious adverse events. PEG-TPOmp is a pegylated TPO peptide agonist and has shown to be effective in animal studies. Similarly, AKR-501 is an orally active TPO agonist and has been shown to be effective in clinical studies involving healthy volunteers. In vitro studies have shown engineered monoclonal antibodies to bind mpl and activate TPO-expressing cell lines. However, all these compounds and drugs need further clinical studies, including in patients with HCV and chronic liver disease before they can be considered for routine use.

Cytokines with thrombopoietic potential: Cytokines such as interleukin-11 (IL-11) has thrombopoietic activity. Recombinant human IL-11 (rhIL-11, Oprelvekin), approved for the management of chemotherapy-related thrombocytopenia, has also been shown to increase platelet count in chronic HCV infection. In a study by Lawitz et al., use of rhIL-11 (Oprelvekin) in patients with advanced liver disease associated with chronic HCV infection caused a 38% increase in mean platelet count from baseline after 12 weeks of therapy, along with an improvement in the mean Knodell Histology Activity Index from 7.3 to 5.9 (p= 0.006). However, the platelet level tends to fall back on discontinuing the drug. It also causes fluid retention in most patients, and this can be a significant management problem in patients with decompensated cirrhosis.
Erythropoietin: The amino-terminal domain on TPO, which binds to thrombopoietin receptor shares significant homology with erythropoietin. Recombinant human erythropoietin (rhEPO) has shown promising results in improving thrombocytopenia in cirrhotic patients. Pirisi et al. studied the effect of rhEPO on the platelet count in 19 patients with thrombocytopenia related to chronic liver disease, and found an increase in mean platelet count by 45% from the baseline in the treatment group as compared to 0% in the placebo group (p < 0.02). As rhEPO has also been suggested for the treatment of ribavirin-induced anemia in patients with HCV, this provides the possibility of using a single drug for the treatment of both thrombocytopenia and anemia related to the INF-based antiviral therapy. However, further studies are needed to confirm this.

Danazol: Danazole used in immune thrombocytopenic purpura may have a role in HCV-related thrombocytopenia. In a study by Alvarez et al., the use of danazol along with the anti-HCV treatment resulted in a 75% increase in the mean platelet count from the baseline and allowed 90% of the patients to complete their antiviral treatment. Anemia, headache, arthralgia and myalgia were some of the common adverse effects of the combination therapy reported in the study.

L-carnitine: L-carnitine is a nutrient synthesized from amino acids lysine and methionine. In a study, the addition of L-carnitine to pegylated-IFN-α plus ribavirin resulted in a decrease in the incidence of thrombocytopenia during antiviral therapy.

Conclusions. Thrombocytopenia in chronic HCV infection has a multifactorial pathophysiology and remains a major problem. The recent change in DAAs without IFN, as the frontline therapy for HCV, permit to avoid the dilemmas associated with initiating or maintaining IFN based anti-viral therapy.

DAAs, with high SVR and less than 1% of hematological adverse effects, have been shown to improve thrombocytopenia associated with HCV infection as well as advanced hepatic disease. While eradication of HCV infection itself is the most practical strategy for the remission of thrombocytopenia, various pharmacological and non-pharmacological therapeutic options, which vary in their effectiveness and adverse effect profiles, are available. Thrombopoietin-mimetic agents like eltrombopag and romiplostim have been shown to be safe and effective for HCV-related thrombocytopenia in various studies.

Studies of the long-term effects of DAA on extrahepatic consequences of HCV infection are in progress.

Acknowledgement. Vijaya Bhatt is supported by the 2016-2017 Physician-Scientist Training Program Grant from the College of the University of Nebraska Medical Center.
disease. Aliment Pharmacol Ther 2007;26 Suppl 1: 13-19. https://doi.org/10.1111/j.1365-2036.2007.03512.x
PMid:17958515

11. Kedia S, Goyal R, Mangla V, Kumar A, S S, Das P, Pal S, Sahni P, Acharya SK: Splenectomy in cirrhosis with hypersplenism: improvement in cytopoenias, Child’s status and institution of specific treatment for hepatitis C with success. Ann Hepatol 2012;11(6): 921-929. PMid:23109457.

12. Adinolfi LE, Giordano MG, Andreana A, Trippodi MF, Urtti R, Cesaro G, Ragone E, Mangoni ED, Ruggiero G: Hepatic fibrosis plays a central role in the pathogenesis of thrombocytopenia in patients with chronic viral hepatitis. British journal of haematology 2001;113(3): 590-599. https://doi.org/10.1046/j.1365-2141.2001.02824.x

13. Giannini E, Borro P, Botta F, Fumagalli A, Maffi F, Podestà E, Romagnoli P, Testa E, Chiambonello B, Pogliato S: Serum thrombopoietin levels are linked to liver function in untreated patients with hepatitis C virus-related chronic hepatitis. Journal of hepatology 2002;37(5): 572-577. https://doi.org/10.1016/S0168-8278(02)00274-X

14. Osada M, Kaneko M, Sakamoto M, Endoh M, Takigawa K, Suzuki-Inoue K, Inoue O, Satoh K, Enomoto N, Yatomi Y: Causes of thrombocytopenia in chronic hepatitis C virus infection. Clinical and Applied Thrombosis/Hemostasis 2012;18(3): 272-280. https://doi.org/10.1177/1076029611429214 PMid:22327815

15. Sulkowski MS: Management of the hematologic complications of hepatitis C therapy. Clinics in liver disease 2005;9(4): 601-616. https://doi.org/10.1016/j.cld.2005.07.007 PMid:16207566.

16. Wang H, Innes H, Hutchinson SJ, Goldberg DJ, Allen S, Barclay ST, Bramley F, Fox R, Fraser A, Hayes PC, Kennedy N, Mills PR, Dillon JF: The prevalence and impact of thrombocytopenia, anaemia and leucopenia on subjected virological response in patients receiving hepatitis C therapy: evidence from a large real world cohort. Eur J Gastroenterol Hepatol 2016;28(4): 394-403. PMid:26695428

17. Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, Kaushansky K: Thrombopoietin. The New England journal of medicine 2011;364(14): 1330-1340. https://doi.org/10.1056/NEJMoa1100670
PMid:21793908

18. Foster GR, Afshari N, Roberts SK, Braun N, Gane EI, Pianko S, Lawitz E, Thompson A, Shiffman ML, Cooper C, Towner WJ, Acharya SK: Splenectomy in cirrhosis with hypersplenism in veterans treated with pegylated interferon plus ribavirin for chronic hepatitis C infection. Pharmacoeconomicsdoi Med Sci 2014;23(5): 480-488. https://doi.org/10.1007/s40887-013-0055-6
PMid:24677630

19. Lin KH, Hsu PI, Yu HC, Lin CK, Tsai WL, Chen WC, Chan HH, Lai KH: Factors linked to severe thrombocytopenia during antiviral therapy in patients with chronic hepatitis C and pretreatment low platelet count. BMC Gastroenterol 2012;12: 7. https://doi.org/10.1186/1471-230X-12-7
PMid:22527364

20. Hermos JA, Quach L, Gagnon DR, Weber HC, Atkinsal A, Cho K, Lawler EV, Grotzinger KM: Incident severe thrombocytopenia in veterans treated with pegylated interferon plus ribavirin for chronic hepatitis C infection. Pharmacotherapy doi Med Sci 2014;23(5): 480-488. https://doi.org/10.1007/s40887-013-0055-6
PMid:24677630

21. Afshari N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, Worikel B, Esteban R: Thrombocytopenia associated with chronic liver disease. J Hepatol 2008;48(6): 1000-1007. https://doi.org/10.1016/j.jhep.2008.03.004 PMid:18433919

22. Schiffer CA, Anderson KC, Bennett CL, Bernstein S, Etting LS, Goldsmith M, Goldstein M, Hume H, McCullough JJ, McIntyre RE: Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19(5): 1519-1538. https://doi.org/10.1200/jco.2000.01.144 PMid:11230098

23. McCormick PA, Murphy KM: Splenomegaly, hypersplenism and coagulation abnormalities in liver disease. Best Practice & Research Clinical Gastroenterology 2000;14(6): 1009-1031. https://doi.org/10.1053/ibmp.2000.00144 PMid:11139352

24. Shah R, Mahour GH, Ford E, Stanley P: Partial splenic embolization. An effective alternative to splenectomy for hypersplenism. The American surgeon 1990;56(12): 774-777. PMid:22681015

25. Akahoshi T, Tomikawa M, Kawanaka H, Furusyo N, Kinjo N, Tsutsumi N, Nagao Y, Hayashi J, Hashizume M, Maehara Y: Laparoscopic splenectomy with interferon therapy in 100 hepatitis-C-virus-cirrhotic patients with hypersplenism and thrombocytopenia. J Gastroenterol Hepatol 2012;27(2): 286-290. https://doi.org/10.1111/j.1440-1746.2011.06870.x PMid:21793908

26. Barcena R, Gil-Grande L, Moreno J, Foruny JR, Oton E, Garcia M, Blazquez J, Sanchez J, Moreno A, Moreno A: Partial splenic embolization for the treatment of hypersplenism in liver transplanted patients with hepatitis C virus recurrence before peg-interferon plus ribavirin. Transplantation 2005;79(11): 1634-1635. https://doi.org/10.1097/01.TP.0000155424.52939.3D PMid:15940057

27. Lebano R, Rosato V, Masarone M, Romano M, Persico M: The effect of antiviral therapy on hepatitis C virus-related thrombocytopenia: a case report. BMC Res Notes 2014;7: 59. https://doi.org/10.1186/1756-0500-7-59 PMid:24457056

PMid:23915622

28. Hernandez F, Blanquer A, Linares M, Lopez A, Tarín F, Cervero A: Autoimmune thrombocytopenia associated with hepatitis C virus infection. Acta haematologica 1998;99(4): 217-220. https://doi.org/10.1159/000099048 PMid:9644300

29. Rajan S, Lieberman HA: Treatment of hepatitis C related
thrombocytopenia with interferon alpha. American journal of hematology 1994;68(3): 202-209. https://doi.org/10.1002/(sici)1551-0665(199403)68:3<202::aid-amj4>3.0.co;2-x PMID:11754404

Afidal NH, McHutchison JG: Review article: pharmacological approaches for the treatment of thrombocytopenia in patients with chronic liver disease and hepatitis C infection. Aliment Pharmacol Ther 2007;25(1): 29-39. https://doi.org/10.1111/j.1365-2036.2007.03511.x PMID:17958517

Vadhan-Raj S, Murray LJ, Bueso-Ramos C, Patel S, Reddy SP, Hoots WK, Johnston T, Papadopoulos NE, Hittelman WN, Johnston DA, Yang TA, Paton VE, Cohen RL, Hellmann SD, Benjamini RS, Broxmeyer HE: Stimulation of megakaryocyte and platelet production by a single dose of recombinant human thrombopoietin in patients with cancer. Ann Intern Med 1997;126(9): 673-681. https://doi.org/10.1097/00000134-199709100-00001 PMID:9139552

Harker LA, Roskos LK, Marzec UM, Carter RA, Cherry JK, Sundell B, Cheung EN, Terry D, Sheridan W: Effects of megakaryocyte growth and development factor on platelet production, platelet life span, and platelet function in healthy human volunteers. Blood 2000;95(8): 2514-2522. PMID:10735829

Basser R. The impact of thrombopoietin on clinical practice. Curr Pharm Des. 2002;8(5):369-377. Review. PubMed PMID: 12069375.

Li J, Yang C, Xia Y, Bertino A, Glaspy J, Roberts M, Kuter DJ: Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood 2001;98(12): 3241-3248. https://doi.org/10.1182/blood.v98.12.3241 PMID:11719360

De Serres M, Ellis B, Dillberger JE, Rudolph SK, Hutchins JT, Boytos CM, Weigl DL, DePrince RB: Immunogenicity of thrombopoietin mimetic peptide GW39058 in BALB/c mice and New Zealand white rabbits: evaluation of the potential for thrombopoietin neutralizing antibody production in man. Stem Cells 1999;17(4): 203-209. https://doi.org/10.1002/1551-7307(199908)17:4<203::aid-stem4>3.0.co;2-8 PMID:10437983

Dower WJ, Cwirla SE, Balasubramanian P, Schatz PJ, Barrett RW, Dower WJ, Cwirla SE, Balasubramanian P, Schatz PJ, Barrett RW, Baccanari DP: Peptide agonists of the thrombopoietin receptor, the thrombopoietin receptor. Stem Cells 1998;16(S1): 21

Kautzky K: Hematopoietic growth factor mimetics. Annals of the New York Academy of Sciences 2001;938(1): 131-138. https://doi.org/10.1111/1749-6632.001582 x PMID:11458500

Broudy VC, Liu NL: AGMS31 stimulates megakaryopoiesis in vitro by binding to Mpl. Cytokine 2004;25(2): 52-60. https://doi.org/10.1016/j.cyto.2003.05.001 PMID:14693160

Bussel JB, Kuter DJ, George JN, McMillan R, Aledort LM, Conklin GT, Lichtin AE, Lyons RM, Nieves J, Wasser JS: AGMS31, a thrombopoiesis-stimulating protein, for chronic ITP. New England Journal of Medicine 2006;355(16): 1672-1681. https://doi.org/10.1056/NEJMoa054626 PMID:17050891

Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Germsheimer TB, Senecal FM, Aledort LM, George JN, Kessler CM, Sanz MA: Efficacy of romiplostim in thrombocytopenic patients with chronic hepatitis C and liver cirrhosis. J Gastroenterol Hepatol 2013;28(2): 335-341. https://doi.org/10.1111/j.1440-3582.2012.07246.x PMID:22849409

Voican CS, Naveau S, Perlemuter G: Successful antithrombotic therapy for hepatitis C virus-induced cirrhosis after an increase in the platelet count with romiplostim: two case reports. Eur J Gastroenterol Hepatol 2012;24(2): 1455-1458. https://doi.org/10.1097/MEG.0b013e32835d7d5f2 PMID:22890208

Erickson-Miller CL, Delorme E, Giampa L, Hopson C, Valoret E, Tian S-S, Masters TG, Keenan R, Rosen J, Dillon S: Biological activity and selectivity for Tpo receptor of the orally bioavailable, small molecule Tpo receptor agonist, SB-497115. Blood 2004;104(11): 2912-2912.
patients affected by HCV treated with Peg interferon-alpha 2b plus ribavirin. World journal of gastroenterology: WJG 2011;17(39): 4414. https://doi.org/10.3748/wjg.v17.i39.4414 PMid:22110268 PMCid:PMC3218156

70. Ikeda M, Fujiyama S, Tanaka M, Sata M, Ide T, Yatsuhashi H, Watanabe H: Risk factors for development of hepatocellular carcinoma in patients with chronic hepatitis C after sustained response to interferon. J Gastroenterol 2005;40(2): 148-156. https://doi.org/10.1007/s00535-004-1519-2 PMid:15770398

71. Moriyama M, Matsunuma H, Aoki H, Shimizu T, Nakai K, Saito T, Yamagama H, Shioda A, Kaneko M, Goto I, Tanaka N, Arakawa Y: Long-term outcome, with monitoring of platelet counts, in patients with chronic hepatitis C and liver cirrhosis after interferon therapy. Interoirology 2003;46(5): 296-307. https://doi.org/10.1159/000073209 PMid:15455850

72. Nagamine T, Ohtuka T, Takehara K, Ari T, Takagi H, Mori M: Thrombocytopenia associated with hepatitis C viral infection. J Hepatol 1996;24(2): 135-140. https://doi.org/10.1016/S0168-8278(96)80021-3

73. Ordi-Ros J, Villareal J, Monegal P, Sauleda S, Esteban I, Villarodell M: Anticardiolipin antibodies in patients with chronic hepatitis C virus infection: characterization in relation to antiphospholipid syndrome. Clin Diag Lab Immunol 2000;7(2): 241-244. https://doi.org/10.1128/cid.7.2.241-244.2000

74. Pynnard T, Schift E, Terg R, Moreno-Otero R, Flamm SL, Schmidt WN, Berg T, Goncales Jr FL, Heathcote J, Diago M: S1000 Results from the Epic3 Program: Platelet Counts Are Strong Predictors of Sustained Viral Response (SVR) in the RE-Treatment of Previous Interferon/Ribavirin Non-Responders (Nt). Gastroenterology 2008;134(4): A-772.

75. Sylvestre DL, Clements BJ: The utility of indirect predictors of hepatitis C viremia. Drug Alcohol Depend 2004;74(1): 15-19. https://doi.org/10.1016/j.drugalcdep.2003.11.006 PMid:15072803

76. Shanmuganathan G, Palaniappan S, Khor B, Radhakrishnan A, Raj P: The clinic-epidemiological pattern of hepatitis C in a tertiary care hospital in Malaysia: the Kuala Lumpur Hospital experience. 6th Asian Pacific Digestive Week (ADPW 2006). Cebu, Philippines 2006.

77. Taliani G, Duca F, Clementi C, De Bac C: Platelet-associated immunoglobulin G, thrombocytopenia and response to interferon treatment in chronic hepatitis C. J Hepatol 1996;25(6): 999. PMid:895477

78. Borroni G, Ceriani R, Cazzaniga M, Tommasini M, Roncalli M, Maltempo C, Felliene C, Salerno F: Comparison of simple tests for the non-invasive diagnosis of clinically silent cirrhosis in chronic hepatitis C. Aliment Pharmacol Ther 2006;24(5): 797-804. https://doi.org/10.1111/j.1365-2036.2006.03034.x PMid:16918883

79. Dalekos GN, Kistis KG, Boumika DS, Vougaris P, Zervou EK, Drosos AA, Tsianos EV: Increased incidence of anti-cardiolipin antibodies in patients with hepatitis C is not associated with aetio-pathogenetic link to anti-phospholipid syndrome. Eur J Gastroenterol Hepatol 2005;17(2): 67-74. https://doi.org/10.1080/09541330500157766 PMid:15665213

80. Kaul V, Friedenberg FK, Brightman LE, Anis U, Zaeer N, Fazili J, Herrine SK, Rothstein KD: Development and validation of a model to diagnose cirrhosis in patients with hepatitis C. Am J Gastroenterol 2002;97(10): 2623-2628. https://doi.org/10.1111/j.1572-0241.2002.06040.x PMid:12385450

81. Luo JC, Hwang SJ, Chang FY, Chu CW, Lai CR, Wang YJ, Lee PC, Tsay SH, Lee SD: Simple blood tests can predict compensated liver cirrhosis in patients with chronic hepatitis C. Hepatogastroenterology 2002;49(44): 478-481. PMid:12385448

82. Prieto J, Yuste JR, Belouqi O, Civeira MP, Riezui J, Aguierre B, Sangro B: Anticardiolipin antibodies in chronic hepatitis C: implication of hepatitis C virus as the cause of the antiphospholipid syndrome. Hepatology 1996;23(2): 199-204. https://doi.org/10.1002/hep.51023021 PMid:8591841

83. Romagnuolo J, Jiangra JS, Jewell LD, Bain VG: Predicting the liver histology in chronic hepatitis C: how good is the clinician? Am J Gastroenterol 2001;96(11): 3165-3174. https://doi.org/10.1111/j.1572-0241.2001.05275.x PMid:11721766

84. Zachou K, Liaskos C, Christodoulou DK, Kardasi M, Papadomou G, Gatselis N, Georgoudou SP, Tsianos EV, Dalekos GN: Anticardiolipin antibodies in patients with chronic viral hepatitis are independent of beta2-glycoprotein I cofactor or features of antiphospholipid syndrome. Eur J Clin Invest 2003;33(2): 161-168. https://doi.org/10.1046/j.1365-2362.2003.01110.x PMid:12588529

85. Hu KQ, Tong MJ: The long-term outcomes of patients with compensated hepatitis C virus-related cirrhosis and history of parenteral exposure in the United States. Hepatology 1999;29(4): 1311-1316. PMid:10094980

86. Kim YS, Lee HS, Ahn YO: Factors associated with positive predictability of the anti-HCV ELISA method with confirmatory RT-PCR. J Korean Med Sci 1999;14(6): 629-634. https://doi.org/10.3346/jkms.1999.14.6.629 PMid:10642940 PMCid:PMC3054447

87. Renou C, Muller P, Jouve E, Bertrand JJ, Raoult A, Bendertier T, Halfon P: Revelance of moderate isolated thrombopenia as a strong predictive marker of cirrhosis in patients with chronic hepatitis C virus. Am J Gastroenterol 2001;96(5): 1657-1659. https://doi.org/10.1111/j.1572-0241.2001.03830.x PMid:11374731

88. Cicardi M, Cesana D, Del Ninno E, Pappalardo E, Sili E, Agostoni A, Colombo M: Prevalence and risk factors for the presence of serum cryoglobulins in patients with chronic hepatitis C. J Viral Hepat 2000;7(2): 138-143. https://doi.org/10.1046/j.1365-2693.2000.00204.x PMid:10760044

89. Lahon P, Ganne-Carrie N, Degos F, Nahon K, Paries J, Grando V, Chaffaut C, Najpom C, Christidis C, Trinchet JC, Chevret S, Beauregard M: Serum albumin and platelet count but not portal pressure are predictive of death in patients with Child-Pugh A hepatitis C virus-related cirrhosis. Gastroenterol Clin Biol 2005;29(4): 347-352. https://doi.org/10.1016/j.jcyg.2005.08.00779. PMid:16558300

90. Wang CS, Yao WJ, Wang ST, Chang TT, Chou P: Strong association of hepatitis C virus (HCV) infection and thrombocytopenia: implications from a survey of a community with hyperendemic HCV infection. Clin Infect Dis 2004;39(6): 790-796. https://doi.org/10.1086/423384 PMid:15472809

91. Alvarez GC, Gomez-Galicia D, Rodriguez-Fragoso L, Marina VM, Dorantes I, Sanchez-Alman M, Mendez-Sanchez N, Esparza JR: Danazol improves thrombocytopenia in HCV patients treated with peginterferon and ribavirin. Ann Hepatol 2011;10(4): 458-468. PMid:21911886

92. Malaguarnera M, Vacante M, Giordano M, Motta M, Bertino G, Pennisi M, Neri S, Malaguarnera M, Li Volti G, Galvano F, L-carnitine supplementation improves hematological pattern in patients affected by HCV treated with Peg interferon-alpha 2b plus ribavirin. World J Gastroenterol 2011;17(39): 4414-4420. https://doi.org/10.3748/wjg.v17.i39.4414 PMid:22110268 PMCid:PMC3218156