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Mini-Review

Thrombocytopenia in Chronic Liver Disease; New Developments

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Abstract

In this mini-review pathophysiology of thrombocytopenia in chronic liver disease (CLD) are discussed with a special emphasises on novel drug therapeutics. Two, recently approved thrombopoietin (TPO) mimetics, lusutrombopag and avatrombopag, provide clinicians a safe and effective alternative to platelet transfusions in CLD patients with thrombocytopenia who are scheduled for an elective invasive procedure. Both TPO mimetics reduced the need for platelet transfusions significantly.

Introduction

Thrombocytopenia is the most common haematological abnormality encountered in patients with chronic liver disease, occurring in 64% to 84% of patients with cirrhosis or fibrosis [1,2]. Among patients undergoing bone marrow biopsies for thrombocytopenia of unknown origin, the prevalence of cirrhosis is as high as 35% [3]. Traditionally, thrombocytopenia has been attributed to hypersplenism, the increased pooling of platelets in the spleen, secondary to portal hypertension [4].

Thrombocytopenia frequently prevents patients from receiving crucial interventions, therapeutic procedures and surgery and is associated with a poor prognosis [5]. Over the past two decades there have been significant advances in the understanding of thrombopoiesis. Recently, the FDA approved two new drugs for thrombocytopenia and chronic liver disease.

In this mini-review pathophysiology of thrombocytopenia in chronic liver disease (CLD) are discussed with special emphasis on novel drug therapeutics.

Pathophysiology

Multiple pathophysiological mechanisms are responsible for thrombocytopenia in CLD and more than one mechanism at a time may account for decreased platelet counts. Decreased levels and activity of the hematopoietic growth factor TPO, hepatic carcinoma, chemotherapy, bone marrow inhibition by excessive alcohol ingestion, hypersplenism secondary to portal hypertension, antiplatelet antibodies and antiviral treatment-induced myelo suppression may all contribute to the development of thrombocytopenia in CLD [6].

Thrombopoeitin (TPO)

There are several important regulators of thrombopoiesis including interleukin (IL) 3,-6 and-11 and steel factor, but TPO is the dominant thrombopoietic hormone. TPO is primarily produced by hepatocytes [7-9] and consists of two domains, an amino-terminal and carboxyl terminal. The amino-terminal shares homology with erythropoietin and binds to the c-Mpl receptor on the surface of megakaryocytes, megakaryocyte progenitor cells, platelets and stem cells [10]. The carboxyl terminal is responsible for the circulating half-life of the hormone, as well as for aiding polypeptide folding [10].

TPO is produced by the liver in humans, whereas the kidneys also contribute in part in animals [11]. TPO is produced at a constant rate irrespective of platelet count. There is no post-transcriptional or translational regulation of TPO production. TPO levels in peripheral blood are regulated through removal by binding to TPO receptors on platelets and megakaryocytes, which leads to increased TPO levels, which reduces platelets and megakaryocytes As a consequence TPO levels rise dramatically in liver-healthy patients with chemotherapy induced thrombocytopenia, while TPO levels remain normal and therefore much too low in cirrhosis associated thrombocytopenia (relative TPO deficiency). Experimental evidence from animal studies show that the amount of TPO provided by the liver and the peripheral platelet count are dependent upon the functional liver cell mass and explain the TPO deficiency in severe liver damage [12].

Animal experiments showed a clear dose-response relationship between TPO or its receptor c-Mpl and peripheral platelet counts when TPO or the c-Mpl receptor has been “knocked out” by homologous recombination [13-15]. In addition, megakaryocyte and peripheral platelet masses were reduced by >80%. Other knock-out studies found that the liver contributed 60% of the TPO required for maintenance of normal platelet count in mice, which could be reversed by transplantation of a wild-type liver [16].

TPO and CLD

Decreased hepatic production of TPO is a critical factor in the development of thrombocytopenia in cirrhosis, the prevalence and severity of thrombocytopenia correlate with the severity of underlying liver disease, particularly the extent of fibrosis [17]. The prevalence of thrombocytopenia is higher in patients with stages 3 and 4 fibrosis when compared to 0-2 fibrosis (64% vs 6%)-[2]. There is an inverse relationship between TPO levels and liver function, as measured by indocyanine green retention and aminopyrine breath tests [18]. Cirrhotic patients with thrombocytopenia have lower levels of circulating TPO than those with normal platelet counts [19].

New Therapeutic Options

Due to advances in the understanding of the biology of thrompoiesis in CLD, the key role of TPO in thrombopoiesis regulation and the changes in TPO production or activity in CLD, a variety of compounds stimulating TPO activity have been developed or are in development, including IL-11,recombinant TPO and other agents.

Recombinant Human Cytokines

Subcutaneous injection of recombinant IL-11 (Neumega, oprelvekin) stimulates progenitor cells and production of megakaryocytes and platelets. rIL-11 has been approved by the FDA for prevention of severe thrombocytopenia following myelosuppressive chemotherapy for solid tumors. However, it can cause significant toxicities, including edema, fluid retention, cardiovascular events and occasionally myalgias and arthralgias [20,21]. Other cytokines (e.g IL-1,LL-3,IL-6) exert potent thrombopoietic activity, but their clinical utility has been severely limited by significant proinflammatory properties that induce flu-like symptoms, including hypotension, fatique and myalgias [21].

Recombinant Human TPO

Although the first generation TPO receptor agonists recombinant human TPO (rh TPO) and pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) were efficacious in clinical trials, clinical development was halted due to the formation of neutralizing autoantibodies that cross-reacted with inactivated endogenous TPO [22-24].

TPO Mimetics

In the last decade several promising TPO agonists with no homology to endogenous TPO have been investigated, primarily for the investigation of chronic immune thrombocytopena (ITP). Recently, the FDA approved lusutrombopag and avatrombag for thrombocytopenia in adults with CLD.

Lusutrombopag (Mulpleta)

Lusutrambopag (Mulpleta, Shionogi, Japan) was approved on July 31, 2018 for thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a medical or dental procedure [25].

Approval was based on two randomized, double-blind, placebo-controlled trials (L-PLUS-1 and L-PLUS-2,NCT02389621) involving 312 patients with CLD and severe thrombocytopenia who were undergoing an invasive procedure and had a platelet count less than 50.000/uL. Patients were randomized 1:1 to receive 3 mg of lusutrombopag or placebo orally once daily for up to 7 days.

In L-PLUS-1 78% of patients (38/49) receiving lusutrombopag required no platelet transfusion prior to the primary invasive procedure, compared with 13% (6/48) who received placebo (95% CI for treatment difference; 49 -79; p<0,0001)-[26].

In L-PLUS-2 65% (70/108) of patients who received lusutrombopag required no platelet transfusion prior to the primary invasive procedure or rescue therapy for bleeding from randomization through 7 days after the procedure compared with 29% (31/107) receiving placebo (95% CI for treatment difference;25%,49%; p<0,0001)- [27].

The most common adverse reaction in 3% of patients was headache. The recommended dose is 3mg orally once daily with or without food for 7 days.

Avatrombopag (Doptelet)

On May 21, 2018 the FDA approved avatrombopag (Doptelet, Aka Rx Inc.) for thrombocytopenia in adults with chronic liver disease scheduled to undergo a procedure.

Approval was based on two international, identically designed, randomized, double-blind, placebo-controlled trials,ADAPT-1 and ADAPT-2. Patients (n=430) with chronic liver disease and thrombocytopenia received either avatrombopag (n=274) or placebo (n=156) daily for 5 days prior to a scheduled procedure, and had at least 1 post-dose safety assessment. Patients were randomized 2:1 to avatrombopag or placebo and stratified according to hepatocellular cancer status and bleeding risk with the elective procedure (low, moderate or high)-[28].

Patients randomized to avatrombopag received differential dosing based on mean platelet count Patients with less than 40.000/uL received avatrombopag 60mg orally once daily for 5 consecutive days. Those with a baseline platelet count of 40.000 to less than 50.000/uL received avatrombopag 40mg orally once daily for 5 consecutive days, Eligible patients were scheduled to undergo their procedure 5 to 8 days after the last dose of study drug.

The primary efficacy endpoint was the proportion of patients or responders who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure.

In the low-baseline platelet cohort,66% and 69% of patients treated with avatrombopag responded in the ADAPT-1 and ADAPT-2 trials, respectively. For those receiving placebo 23% (treatment difference 43%; 95% CI;27-38; p<0,0001) and 35% (treatment difference 34%; 95% CI;16-52; p=0,0006) responded in the ADAPT-1 and ADAPT-2 trials, respectively.

In the high-baseline platelet cohort, 88% of avatrombopag-treated patients in both trials responded compared to 38% and 33% of placebo-treated patients. Treatment difference was 50% (95% CI; 32-68; p<0,0001) in the ADAPT-1 and 55% (95% CI;37-73; p<0,0001 in the ADAPT-1 and 58% (95% CI; 37-73; p,0,0001) in the ADAPT-2 trial [29].

Conclusion

A better understanding of the biology of thrombopoiesis in patients with chronic liver disease (CLD) has lead to the development of effective thrombopoietin (TPO) mimetics. Both lusutrombopag and avatrombopag reduced the need for platelet transfusions significantly in CLD patients with thrombocytopenia, who are scheduled for an elective invasive procedure. These drugs provide physicians a safe and effective alternative to platelet transfusions in the clinical management of these patients.

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