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Correction of Thrombocytopenia with Thrombopoietin Receptor Agonists in Patients with Liver Cirrhosis Before Elective Surgery or Invasive Procedures

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Aim: to review the pathogenesis of thrombocytopenia and possible ways of its correction in patients with liver cirrhosis before elective surgical interventions or invasive procedures to optimize clinical practice.
Key points. Thrombocytopenia is a common hematological complication of liver cirrhosis, affecting up to 75–86 % of patients with decompensated cirrhosis. Thrombocytopenia is associated with increased risks of bleeding and mortality. It complicates the management of patients, especially those who require invasive procedures, many of which carry a risk of bleeding. This risk of bleeding varies with the severity of thrombocytopenia, coagulation status, and type of invasive procedure.
Moderate-to-severe thrombocytopenia can interfere with life-saving interventions, such as invasive procedures/surgeries. Delayed care is associated with longer hospital stays and greater medical costs. Thrombopoietin receptor agonists (avatrombopag) should be considered for the management of cirrhotic patients with severe thrombocytopenia undergoing elective invasive interventions with a high risk of bleeding.
Conclusion. Thrombopoietin receptor agonists (avatrombopag) have demonstrated high efficacy and safety and are considered a promising first-line option for the management of severe thrombocytopenia in patients with liver cirrhosis undergoing elective surgical interventions or invasive procedures.
Keywords: liver cirrhosis, platelet, thrombocytopenia, thrombopoietin, thrombopoietin receptor agonists, avatrombopag, chronic liver disease, bleeding, hemostasis, surgical interventions, invasive procedures
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Коррекция тромбоцитопении у пациентов с циррозом печени агонистами рецептора тромбопоэтина перед плановыми хирургическими операциями или инвазивными процедурами

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Цель обзора: рассмотрение звеньев патогенеза тромбоцитопении и возможные пути ее коррекции у пациентов с циррозом печени перед плановыми инвазивными процедурами или хирургическими вмешательствами для оптимизации клинической практики.
Основные положения. Одним из наиболее частых гематологических осложнений у пациентов с циррозом печени является тромбоцитопения, которая наблюдается в 75–86 % случаев на стадии декомпенсации. Тромбоцитопения связана с повышенным риском кровотечений и смертности, она усложняет ведение таких пациентов, особенно перед проведением инвазивных процедур, многие из которых дополнительно сопряжены с риском кровотечения. Последний, в свою очередь, зависит от степени тромбоцитопении, состояния гемостаза пациента и типа инвазивного вмешательства.
Тромбоцитопения умеренной и тяжелой степени может препятствовать оказанию пациентам жизненно важных вмешательств, таких как инвазивные процедуры / операции. Отсроченное оказание медицинской помощи может увеличить время госпитализации и общие затраты на медицинское обслуживание. Для коррекции тяжелой степени тромбоцитопении у пациентов с циррозом печени при подготовке к плановому инвазивно-

му вмешательству с высоким риском кровотечений рекомендовано рассмотреть возможность использования агонистов рецептора тромбопоэтина (аватромбопаг).
Заключение. Агонисты рецептора тромбопоэтина (аватромбопаг) продемонстрировали высокую эффективность и безопасность среди пациентов с циррозом печени перед плановыми инвазивными процедурами или хирургическими вмешательствами, что позволяет рассматривать их как перспективные препараты первой линии выбора для коррекции тяжелой тромбоцитопении в данной группе пациентов.
Ключевые слова: цирроз печени, тромбоциты, тромбоцитопения, тромбопоэтин, агонисты рецептора тромбопоэтина, аватромбопаг, кровотечение, гемостаз, инвазивные процедуры, хирургические вмешательства
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Liver cirrhosis (LC) is the terminal stage of most chronic liver diseases. LC (derived from the Greek word "*kirrhos*" — orange) is characterized by diffuse fibrosis and transformation of the normal liver structure with the formation of nodules [1].

Thrombocytopenia is a common hematological complication of progressive chronic liver diseases, occurring in both compensated and decompensated disease stages.

In clinical practice, the peripheral platelet count is a reliable marker of primary hemostasis in patients with LC. Thrombocytopenia (platelet count $< 150 \times 10^9$/L) is a common laboratory finding at the early stage of LC found by accident. Most patients with compensated LC report no complaints, are asymptomatic, and may have a good quality of life for several years. Thrombocytopenia is a laboratory marker of the preclinical stage of LC. Thrombocytopenia is associated with complex changes in hemostasis occurring in patients with progressive liver failure and decompensation.

Clinically, thrombocytopenia may manifest with hemorrhagic syndrome (petechiae, cutaneous and mucosal ecchymoses, nasal, gingival, uterine, gastrointestinal bleeding, etc.).

The prevalence of thrombocytopenia is 6 % in patients with the pre-cirrhotic stage of chronic liver diseases [2], increasing up to 75–86 % in patients with progressive liver fibrosis or cirrhosis [3, 4].

Thrombocytopenia is categorized according to the plasma platelet count [4]:

- **mild:** platelet count between 100 and 150×10^9/L (100,000–150,000/μL);
- **moderate:** platelet count between 50 and 100×10^9/L (50,000–100,000/μL);
- **severe:** platelet count below 50×10^9/L (< 50,000/μL).

The risk of moderate-to-severe thrombocytopenia is 12-fold higher in patients with LC compared with those without LC [5].

A study enrolling 1,600 patients documented that the median platelet count on admission was approximately 130×10^9/L. Of these, 60 %, 35 %, and 10 % had mild, moderate, and severe thrombocytopenia, respectively [6].

Thrombocytopenia may worsen with increasing disease severity and can be used as a marker of progressive liver disease. Severe thrombocytopenia may be a strong independent predictor of bleeding and mortality [7]. Although spontaneous bleeding is unlikely in a patient with mild-to-moderate thrombocytopenia, monitoring of plasma factors is also required. Decreasing platelet counts correlate with the risk of bleeding, with the strongest correlation noted for platelet counts $< 10 \times 10^9$/L (a high risk of spontaneous bleeding and mortality) [5, 8].

In patients with LC, spontaneous massive bleeding may be related to severe thrombocytopenia, as well as to other serious disorders of the hemostatic system, including combined disorders of the megakaryocyte-platelet system, clotting factors, and fibrinolysis [8].

There are numerous pathophysiological factors of LC-associated thrombocytopenia, including (Fig. 1):

1) splenomegaly and hypersplenism, with increased deposition (sequestration) of circulating platelets in the spleen;

2) reduced synthesis of thrombopoietin in the liver (and possibly in the kidneys), with decreased production and release of platelets from bone marrow due to the reduced stimulation of megakaryocytopoiesis and thrombocytopoiesis;

3) increased destruction of platelets (hyperfibrinolysis, sepsis, etc.).

Normally, about 1/3 of the platelet population is found in the spleen. The lifespan of circulating platelets is about 10 days. Thrombocytopenia is a result of splenic sequestration of circulating platelets caused by congestive splenomegaly as a result of portal hypertension. The enlarged spleen

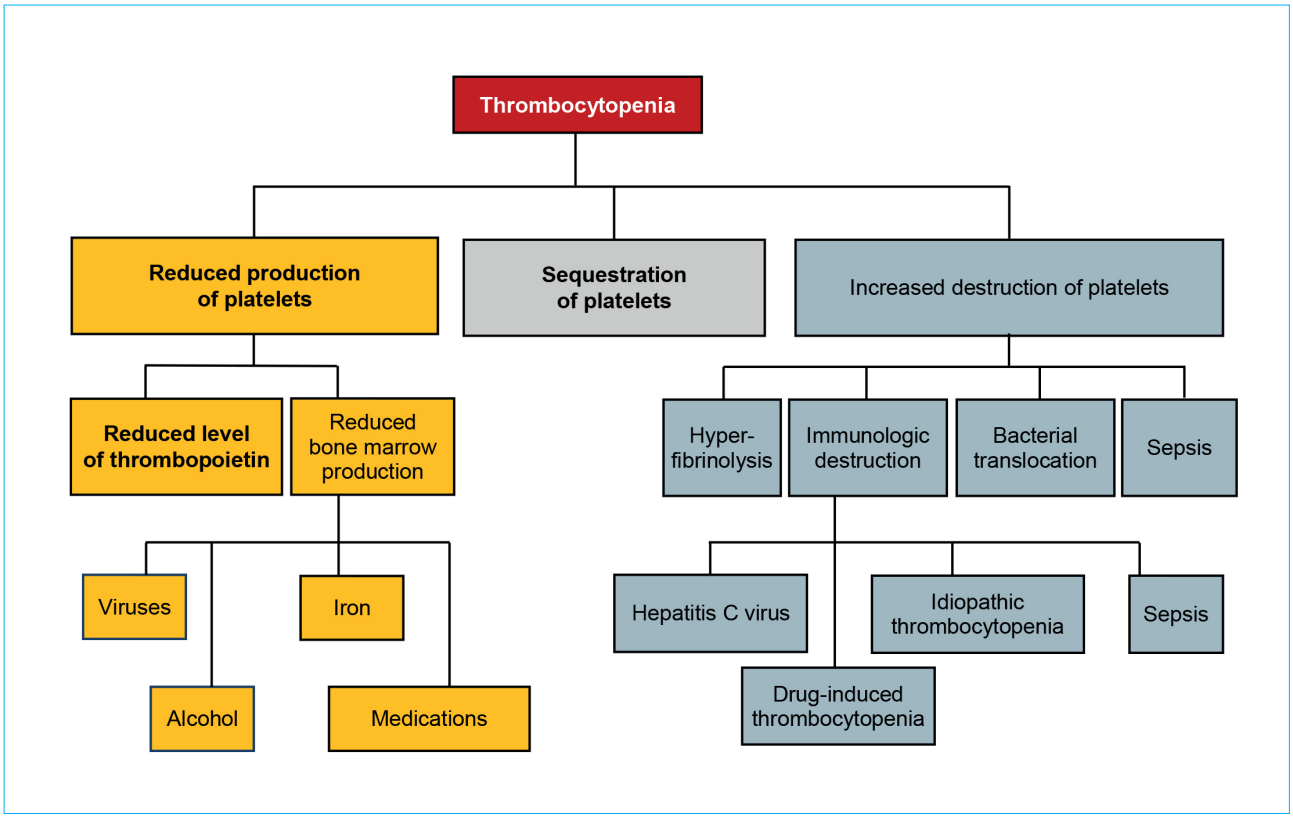

Figure 1. Pathophysiological processes of thrombocytopenia development in patients with liver cirrhosis

Рисунок 1. Патофизиологические процессы развития тромбоцитопении у пациентов с циррозом печени

can accumulate up to 80–90 % of platelets, while their life expectancy does not change.

Patients with progressive severe chronic liver diseases and/or LC have rebalanced hemostasis that triggers compensatory mechanisms with a labile, extremely unstable equilibrium. This condition can be characterized as a balanced low-level hemostatic equilibrium due to a concordant reduction in pro- and anti-hemostatic components. Decreasing levels of procoagulant proteins are counterbalanced by decreasing levels of natural anticoagulants and antifibrinolytic proteins, and elevated plasma levels of von Willebrand factor and platelet adhesion proteins can compensate for thrombocytopenia [2, 4]. However, this balance can be destabilized by various triggers (e.g., infection, variceal bleeding, decompensated LC, invasive procedures, or inadequate transfusions).

It is also necessary to be aware of pseudothrombocytopenia [8]. This is a falsely determined low platelet count in vitro when ethylenediaminetetraacetic acid (EDTA) interacts with blood in a test tube. As a result, platelet aggregates are formed under the action of EDTA-dependent antiplatelet antibodies [4, 9, 10]. To rule out pseudothrombocytopenia, the blood smear should be tested for clots, and the complete blood count should be repeated using other anticoagulants (heparin or sodium citrate) [4].

The international professional community believes that it is inappropriate to study the functional properties of platelets in clinical practice in patients with LC [4, 11]. In this group of patients, severe thrombocytopenia may be accompanied by an increase in the prothrombotic properties of platelets due to an increase in the concentration of von Willebrand factor and a decrease in ADAMTS13 (A disintegrin-like and metalloproteinase with thrombospondin-1-like domains, member 13) [4].

Reduced hepatic production of thrombopoietin together with direct bone marrow suppression, e.g. due to toxic, drug- or virus-induced suppression of megakaryocytopoiesis, is thought to be key factors in the development of LC-associated thrombocytopenia [2, 8]. Therefore, the treatment of LC-associated thrombocytopenia should be based on eliminating its cause and addressing its pathophysiology. Thrombopoietin receptor agonists (TPO-RAs) are considered a promising treatment option for thrombocytopenia.

Thrombopoietin is a glycoprotein produced primarily in the liver, with small amounts of

thrombopoietin made by the kidney. Thrombopoietin regulates the differentiation of megakaryocytes and platelets. Interestingly, thrombopoietin is the only cytokine that stimulates both megakaryocytopoiesis and thrombopoiesis at all stages of differentiation and maturation (from stem cells to platelets).

There is a direct correlation between the levels of circulating thrombopoietin, thrombocytopenia grade, and LC stage [2].

There still has been no consensus on whether thrombocytopenia should be treated in order to prevent spontaneous bleeding in patients with LC. Normally, coagulation disorders require treatment in patients with LC prior to invasive procedures or surgical interventions or after recent bleeding. Thrombocytopenia complicates the management of patients with LC undergoing invasive procedures due to the high risk of bleeding, which varies according to the thrombocytopenia grade, coagulation status, and type of the invasive procedure. Thrombocytopenia can impede life-saving surgeries and cause delayed medical care, thus prolonging hospital stays and increasing medical costs.

In 2024, the Russian Society for the Study of the Liver (RSSL) issued a consensus document on the correction of thrombocytopenia in patients with liver cirrhosis before elective surgical interventions or invasive procedures [4]. This document covers the following:

– main issues of risk stratification of hemorrhagic complications;

– the prognostic value of thrombocytopenia;

– the necessity and methods of drug correction of various degrees of thrombocytopenia and reducing the risk of hemorrhagic complications in patients with LC.

Experts have developed tables that define the recommended minimum threshold level of platelets for performing elective surgical interventions/invasive procedures in patients with LC, considering the risk of hemorrhagic complications (low or high).

In addition to platelet count, the following factors affect the risk of periprocedural/perioperative bleeding:

- the nature and scope of the intervention itself;
- plasma hemostasis, closely associated with liver function and the severity of liver cirrhosis;
- systemic factors (sepsis; acute kidney injury; acute-on-chronic liver failure, ACLF, etc.);
- experience of a surgeon/surgical team;
- severity of liver cirrhosis (MELD > 25) and patients' overweight (BMI $\geq$ 40 kg/m^2);
- medical history (taking antiplatelet agents, anticoagulants, and any medications that may potentially affect hemostasis);
- individual characteristics of the patient, including genetic characteristics.

Assessing the risks of perioperative hemorrhagic complications in patients with LC the bleeding risks associated with invasive/surgical procedures/interventions can be divided into low or high [4].

Procedures with a *low risk* of predicted bleeding are those in which severe bleeding is possible in *< 1.5 %* of cases and/or if it does occur, it can be easily stopped.

Procedures with a *high risk* of predicted bleeding are those in which severe bleeding is likely to occur in *> 1.5 %* of cases and/or in which it will be difficult to stop or if the bleeding leads to irremediable consequences (for example, bleeding in the central nervous system and a high risk of subsequent disability) [4].

The experts have faced with an important task of stratifying the risks of perioperative (occurring during/after surgery) or periprocedural (occurring during/after an invasive procedure) hemorrhagic complications in patients with LC based on literature data and their own long-term experience. For this purpose, all **elective surgical interventions** were grouped depending on the anatomical area and the degree of risk of bleeding. For example, to perform elective cholecystectomy, the minimum platelet count in patients with LC should be > 100 × 10^9/L [4]. All **elective invasive procedures** were grouped into endoscopic, intercutaneous/vascular, dental and depending on the degree of risk of bleeding. For example, elective laparocentesis (paracentesis) may not be bearing risks for patients with LC and platelet count > 30 × 10^9/L, while elective liver biopsy is recommended only for patients with moderate thrombocytopenia (platelet count > 80 × 10^9/L) [4]. More detailed information can be found in the prepared by specialists' consensus document on the correction of thrombocytopenia in patients with cirrhosis of the liver before elective surgical interventions/invasive procedures [4].

Platelet transfusion is commonly used for the clinical management of severe thrombocytopenia in patients with LC undergoing invasive interventions. However, the use of platelet transfusion may be limited by the development of antiplatelet antibodies, short duration of storage and efficacy, risk of infection and other transfusion-related complications, high costs, difficult production and transportation, intravenous route of administration that necessitates hospitalization [11].

TPO-RAs can be a promising alternative treatment for severe thrombocytopenia in patients with LC undergoing elective invasive interventions. TPO-RAs have several advantages: formulated as

tablets, they can be taken at home, raise platelet levels for a longer period (+3 weeks), have a good safety profile (number of adverse events comparable to that for placebo) and a more predictable effect [11–13].

An algorithm for the assessment of thrombocytopenia and the risk of bleeding, and proposed management of thrombocytopenia in patients with chronic liver diseases or LC undergoing elective invasive interventions is shown in Figure 2.

Currently, several TPO-RAs are registered on the world market: eltrombopag, avatrombopag, lusutrombopag and romiplostim. The latter is included in the treatment protocols for immune thrombocytopenia only. In Europe, for the management of severe thrombocytopenia in patients with chronic liver diseases or LC undergoing surgery there are used two agents: avatrombopag and lusutrombopag. Avatrombopag has been authorized in the Russian Federation for this indication.

Avatrombopag is an oral, low-molecular-weight, non-peptide TPO-RA that stimulates the proliferation and differentiation of megakaryocytes from bone marrow progenitor cells, thus increasing platelet production. Avatrombopag mimics the biological effect of thrombopoietin by acting on the transmembrane part of its receptor (c-Mpl), leaving free the thrombopoietin binding site (different binding sites) (Fig. 3). Avatrombopag is believed to potentiate the action of endogenous thrombopoietin (an additive effect), increasing platelet production. Avatrombopag has demonstrated a high safety profile (low risk of thromboembolic events and hepatotoxicity comparable with placebo) [18] and does not have the side effects of eltrombopag which has limited use in patients with chronic liver diseases and LC.

The efficacy and safety of avatrombopag have been confirmed in two multicenter, placebo-controlled, randomized phase 3 clinical

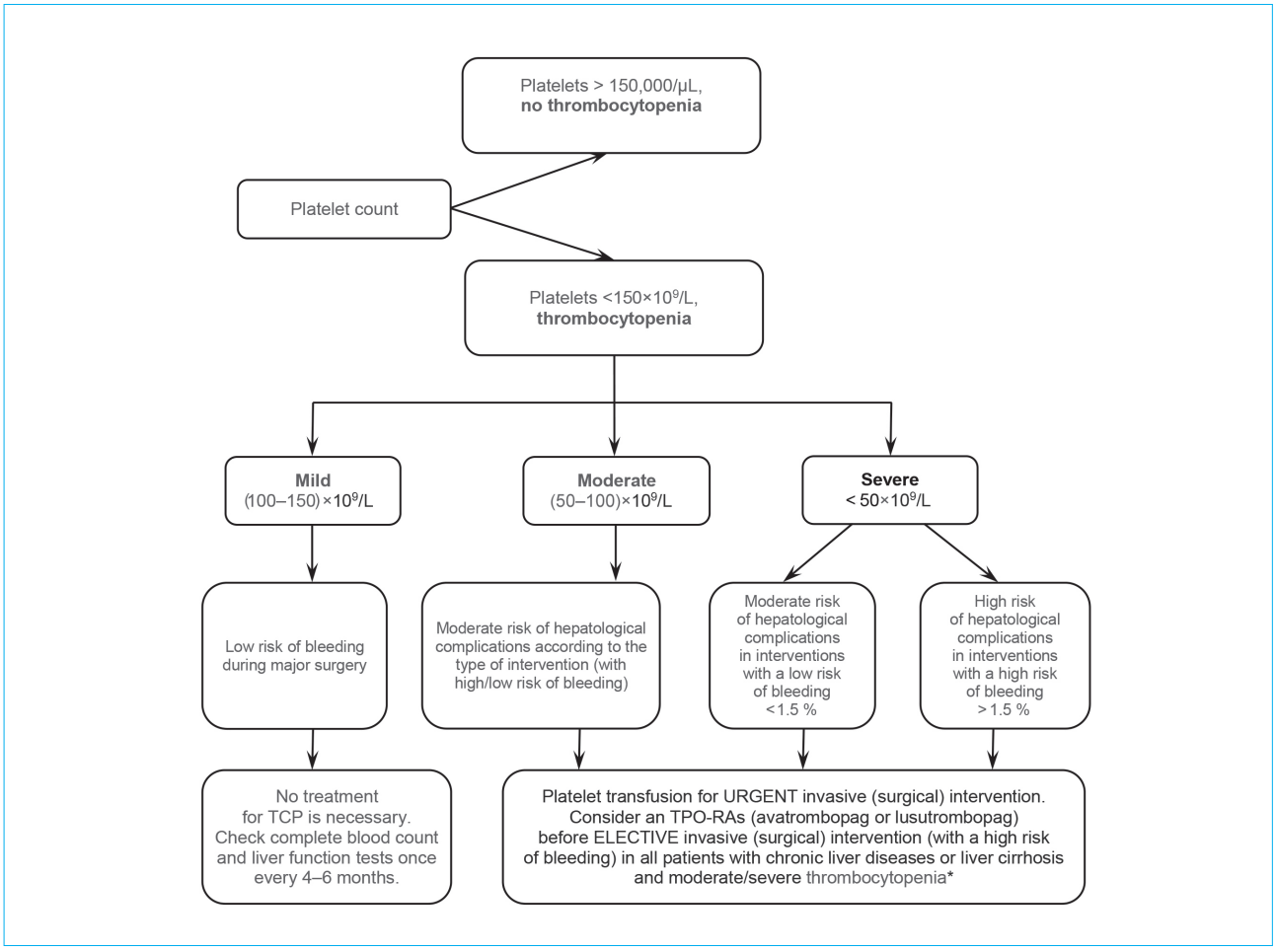

Figure 2. Algorithm for assessing the degree of thrombocytopenia, the risk of bleeding in patients with chronic liver disease/cirrhosis and possible treatment tactics; * — an individual approach to therapy is always required

Рисунок 2. Алгоритм оценки степени тромбоцитопении, риска кровотечений у пациентов с хроническими заболеваниями печени / циррозом печени и возможная лечебная тактика; * — всегда требуется индивидуальный подход к терапии

trials — ADAPT-1 and ADAPT-2. A total of 435 patients were included in the study, of whom 277 patients received avatrombopag and 158 patients received placebo. An analysis of consolidated data from phase 3 ADAPT-1 and ADAPT-2 clinical trials demonstrated that avatrombopag was superior to placebo both in the overall study population and across subgroups with different baseline platelet counts. In the avatrombopag group, the proportion of patients who did not require platelet transfusion or rescue therapy for bleeding was higher when in the placebo group [11, 14, 15].

Adult patients with chronic liver disease (MELD ≤ 24) and severe thrombocytopenia (< 50 × 10^9/L at the inclusion stage) were stratified into two groups: the first group included patients with platelet concentrations < 40 × 10^9/L, the second group included patients with platelet concentrations in the range from 40 to 50 × 10^9/L. The groups were further divided into main and control (placebo) subgroups. The main subgroup received a dose of avatrombopag depending on the initial platelet count: at a concentration of < 40 × 10^9/L — 60 mg of medication per day, from 40 to 50 × 10^9/L — 40 mg per day. The

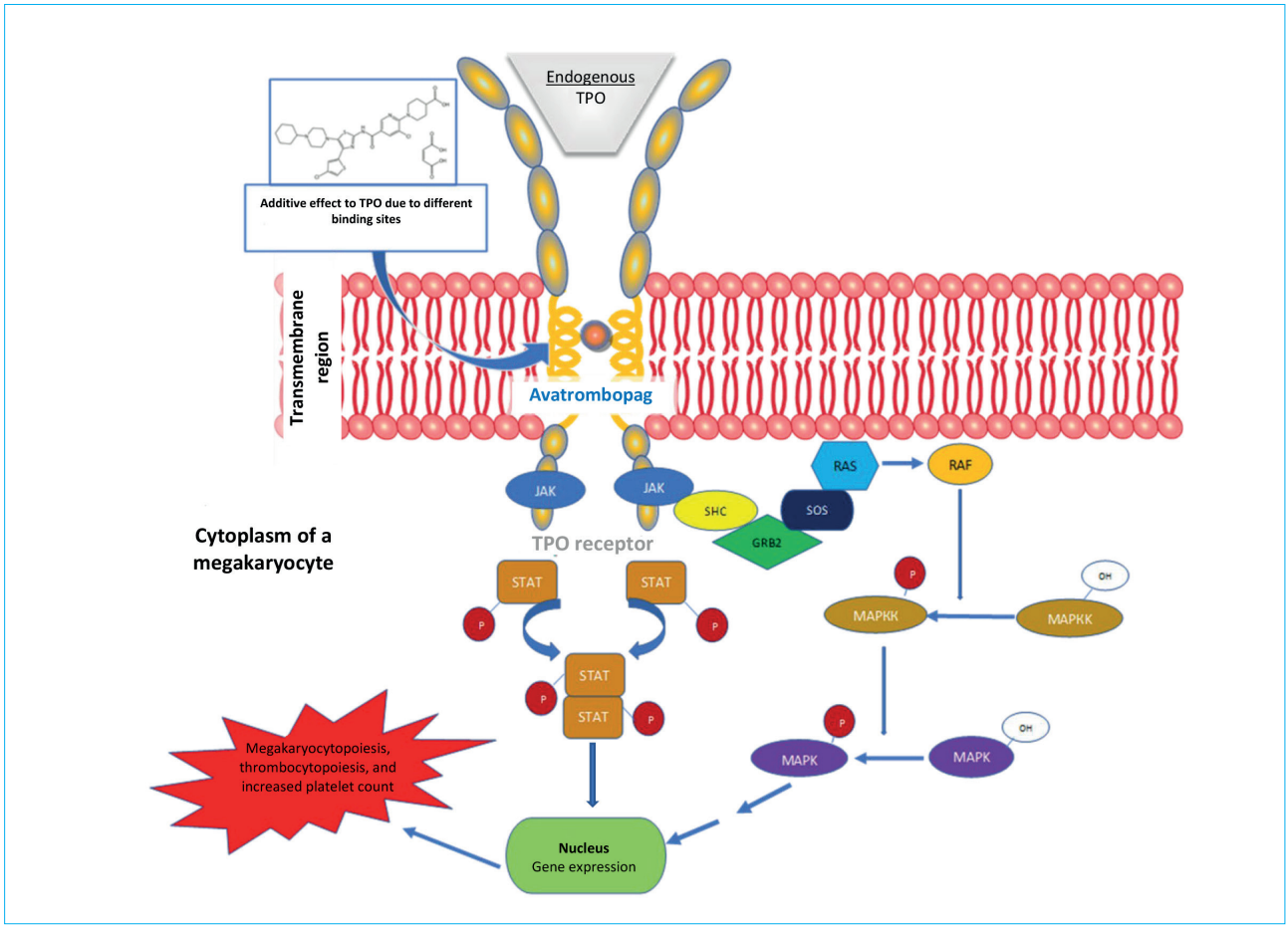

Figure 3. Scheme of signal transmission during the interaction of thrombopoietin with the receptor and its agonist (avatrombopag): TPO — thrombopoietin; JAK — Janus kinases; STAT — signal transducer and activator of transcription; P — phosphorylated form of protein; OH — dephosphorylated form of protei; SHC — Src family kinase; GRB2 — growth factor receptor-bound protein 2; SOS (Son of sevenless) — RAS-acting guanine nucleotide exchange factor; RAS and RAF — components of the signaling pathway that activates MAPKK; MAPKK — mitogen-activated protein kinase kinase; MAPK — mitogen-activated protein kinase

Рисунок 3. Схема передачи сигнала при взаимодействии тромбопоэтина с рецептором и его агонистом (аватромбопаг): TPO (thrombopoietin) — тромбопоэтин; JAK (Janus kinases) — Янус-киназа; STAT (signal transducer and activator of transcription) — сигнальный белок-трансдуктор и активатор транскрипции; P — фосфорилированная форма белка; OH — дефосфорилированная форма белка; SHC (Src family kinase) — киназа семейства Src; GRB2 (growth factor receptor-bound protein 2) — белок, связанный с рецептором фактора роста 2; SOS (Son of sevenless) — фактор обмена гуаниновых нуклеотидов, действующих на RAS; RAS и RAF — компоненты сигнального пути, активирующего MAPKK; MAPKK (mitogen-activated protein kinase kinase) — киназа митоген-активируемой киназы; MAPK (mitogen-activated protein kinase) — митоген-активируемая киназа

control subgroup received a placebo. The course of treatment was 5 days. Scheduled operations/interventions were performed 5–8 days after taking the last dose of the medication or placebo. The effectiveness of treatment was assessed by such criteria as the proportion of patients who did not require platelet concentrate transfusions or other urgent measures due to peri- or postprocedural bleeding within 7 days after the elective and performed intervention.

An analysis of the combined data from the two ADAPT studies showed that avatrombopag was significantly more effective than placebo in reducing the need for platelet concentrate transfusions or other urgent transfusion measures: 66.9 % vs. 28.6 % in the group with an initially low and 88 % vs. 35.8 % in the group with an initially high platelet count ($p < 0.0001$ for each group). It is important to note that in the majority of patients (93.8 %) who received avatrombopag, the platelet count on the day of the procedure was $\geq 50 \times 10^9$/L compared to 38.0 % of patients from the placebo group [14].

A subanalysis of the ADAPT-1 and ADAPT-2 studies showed that avatrombopag was equally effective in invasive procedures/surgical interventions of any risk of bleeding degree. The effectiveness of the avatrombopag was not affected by the patient's gender, age, ethnicity, etiology, or severity of LC according to the Child — Pugh or MELD scores [14, 15].

In patients with chronic liver diseases and severe thrombocytopenia, TPO-RA therapy was associated with a doubling of the mean platelet count by the day of the invasive procedure, with a gradual decrease to the baseline level by day 35 [14]. On day 17 the mean platelet count was approximately 50×10^9/L or higher, and three patients had a platelet count > 200×10^9/L [15].

Information on the use of TPO-RA (avatrombopag) in patients with chronic liver diseases or LC in preparation for elective invasive/surgical interventions is supplemented by data from a phase 4 observational cohort study (real clinical practice) published in 2023 [16]. In this study, avatrombopag treatment was well tolerated, increased the average platelet count by the day of the procedure, and reduced the need for intraoperative platelet concentrate transfusion. Avatrombopag caused no treatment-related side effects, and there were no thromboembolic complications or deaths during the study.

The onset of the platelet count increase was observed within 3 to 5 days, with the peak effect observed after 10 to 13 days [17]. The recommended daily dose of avatrombopag is based on the initial platelet count and is 40 or 60 mg for 5 days with food. Dosing should begin 10 to 13 days before the elective invasive intervention which should be performed 5 to 8 days after the last dose of avatrombopag [18].

After 3–5 days, the mean increase in the platelet count is 30×10^3, with a dose-dependent effect. Avatrombopag may be used as a locoregional therapy of hepatocellular carcinoma in patients without portal vein thrombosis [19].

Thus, oral TPO-RAs (in the Russian Federation avatrombopag is used) are a preferable option compared with platelet transfusions due to the ease and safety of their use in clinical practice. TPO-RAs should not be used to treat bleedings in patients with LC. In these cases, thrombocytopenia is managed according to the current standards of local and systemic hemostasis.1

Contraindications to TPO-RAs may include past thrombotic complications [18], including portal vein thrombosis. TPO-RAs are not recommended for patients with immune thrombocytopenia associated with coronavirus infection (COVID-19) due to the high risk of thrombosis [20].

Conclusion

Thrombocytopenia is a common hematological abnormality in LC, affecting up to 75–86 % of patients. Platelet sequestration in the enlarged spleen and thrombopoietin deficiency are key mechanisms of LC-associated thrombocytopenia.

Treatment of thrombocytopenia in order to prevent spontaneous bleeding is debatable due to the lack of evidence.

When evaluating the risk of peri- or postoperative bleeding, many factors are taken into account and currently it is necessary to be guided by an expert consensus document that will help practitioners in clinical practice in the management of such patients [4]. When routinely preparing patients with cirrhosis of the liver for invasive/surgical interventions with various risks of hemorrhagic complications, it may be advisable to correct severe thrombocytopenia using oral low-molecular-weight thrombopoietin receptor agonists. Compared to placebo, the use of TPO-AR (avatrombopag) led to a statistically significant increase in the number of platelets, a decrease in the frequency of platelet concentrate transfusions, and a decrease in the overall frequency of bleeding during/after invasive/surgical interventions/procedures, without increasing the frequency of thrombosis.

Thus, second-generation thrombopoietin receptor agonists may become the new standard of treatment of thrombocytopenia in patients with chronic liver diseases or LC who are preparing for elective invasive procedures or surgical interventions. Further research in this area is required.

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