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Research progress of rivaroxaban in portal vein thrombosis in liver cirrhosis

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Abstract: Among the complications related to liver cirrhosis, portal vein thrombosis (PVT) occupies an important position and has a high incidence. As a new type of direct oral anticoagulant, rivaroxaban directly targets the active site of coagulation factor Xa and ultimately achieves the purpose of anticoagulation by inhibiting the activity of thrombin. Compared with traditional anticoagulants, rivaroxaban has more advantages and has been widely used in clinical practice. And a number of clinical studies have verified its efficacy and safety in the treatment of PVT in liver cirrhosis. This article reviews the application and progress of rivaroxaban in the treatment of portal vein thrombosis in liver cirrhosis, in order to help clinicians to improve their understanding of rivaroxaban anticoagulation.

1. Introduction

Portal vein thrombosis (PVT), as a vascular obstructive disease, is primarily characterized by thrombotic lesions in the main trunk of the portal vein and its branches (left and/or right), with or without involvement of the mesenteric and splenic veins [1].As a common vascular complication in the process of liver cirrhosis, the incidence of PVT in cirrhotic patients is also significantly higher than that in the general population, according to the literature, its incidence reaches 1%~25%, and the risk of this complication increases with the aggravation of the degree of cirrhosis[2],in patients with cirrhosis in the compensated stage, the probability of the occurrence of PVT is generally in the range of 1%~10%, and the probability of occurrence can be as high as 26% for patients with decompensated cirrhosis [3].The development of PVT exacerbates the risk of bleeding, ascites, and mortality in cirrhotic patients [4],Therefore, timely anticoagulation therapy is crucial for preventing the progression of both PVT and liver cirrhosis. As new direct-acting oral anticoagulants (DOACs), rivaroxaban is widely used in clinical practice because it is easy to administer, has a fast onset of action, and does not require monitoring of the international normalized ratio (INR).However, due to the poor liver reserve function and coagulation function of patients with cirrhosis, whether to perform anticoagulation, when to perform anticoagulation, and whether there is a risk of rebleeding during the anticoagulation process are all things that need to be paid attention to.

2. Pathogenesis of PVT in liver cirrhosis

The mechanism of PVT complicating cirrhosis is highly complex and multifactorial, and has not yet been fully understood by the medical field. The formation of PVT is usually regarded as a result of the synergistic effect of hemodynamic alterations (e.g., slowing down of blood flow), vascular endothelial damage, and abnormally high blood coagulability, and this theory is also applicable to the progression of PVT in cirrhosis. The common risk factors for cirrhotic PVT are manifold, such as decreased blood flow in the portal vein system, local vascular damage due to abdominal surgery, hereditary or acquired abnormalities of coagulation (i.e., thrombophilia), and inflammation of the portal vein, abdominal organs, and intestinal mucosa[1]. Among the above risk factors, the slowing down of portal blood flow is widely recognized as the most critical pathogenic factor in the process of cirrhosis complicated with PVT[5],and its pathophysiological mechanism lies in the fact that, when there is an abnormal proliferation of fibrous tissues and destruction of hepatic sinusoidal structure in the liver tissues of patients with cirrhosis, the resistance of intrahepatic circulatory system will be significantly increased, and this change directly results in the slowing down of blood flow rate within the portal vein system trend [6].Numerous studies have shown that when blood flow velocity in the portal vein of cirrhotic patients falls below the critical value of 15 cm/s as indicated by Doppler ultrasound, the probability of developing PVT rises significantly, and the risk may increase up to 10-20 times [7， 8]. In addition, the use of non-selective beta-blockers (NSBB) can also result in a further reduction of blood flow in the portal venous system, and a meta-analysis of multiple studies [5] showed that the risk of PVT in cirrhotic patients treated with NSBB may be increased to 4.62 times. In another prospective study [9],after correction and analysis of multiple factors, it was found that the use of NSBB did not increase the risk of PVT, and there was no correlation between the two. Therefore, NSBB, as the main drug for the treatment of portal hypertension, can not be easily stopped, but good regular monitoring is also necessary. In addition to these reasons, with the change of patient's physical condition and living environment, the factors that induce the formation of PVT in patients are also increasing, and it is not excluded that these factors exist at the same time.

3. Staging and clinical manifestations of PVT in liver cirrhosis

For the classification of the formation time of PVT, the American Academy of Liver Diseases [10]categorizes PVT into two types: recent thrombosis and chronic thrombosis, the duration of recent thrombosis is less than 6 months, and the patients tend to have symptoms such as abdominal pain, fever, etc., while the duration of chronic thrombosis is longer, usually more than 6 months, and in the clinical observation, most of the patients with chronic PVT will not have obvious abnormal symptoms. However, in cases of PVT complicated by liver cirrhosis, the diagnosis often stems from patients' regular cirrhosis progression assessment and liver cancer screening process, and the specific diagnosis is mainly based on the results of imaging tests. Due to the hidden characteristics of the onset of this disease in daily life scenarios and the lack of specific manifestations, it is difficult to accurately define the exact time of the formation of PVT. Based on the integration of clinical diagnosis and treatment standards and the experience of various experts, China's "Expert Consensus on the Management of Portal Vein Thrombosis in Liver Cirrhosis (2020 Edition)" [1] proposes that clinical diagnosis needs to be assessed according to the staging of whether the patient has the clinical manifestations related to the presence of PVT, and that when the patient has the manifestations of acute abdominal pain, nausea, vomiting, etc., the patient is diagnosed as acute symptomatic PVT, and this staging of PVT can easily lead to ischemic lesions of mesenteric membrane, which can lead to severe mesenteric ischemic lesions. This stage of PVT is prone to ischemic lesions of the mesentery, which may lead to life-threatening complications such as necrosis of the intestinal tube in severe cases. If the above signs

and symptoms are absent, then the diagnosis can be made as non-acute symptomatic PVT, which has no acute symptoms but may cause spongy or complete occlusion of the portal system in the long term, which may lead to the development of secondary portal hypertension syndrome. This staged diagnostic model can help clinicians to help patients develop individualized treatment plans for different pathological stages, which is an important guideline to improve patients' lives and enhance prognosis.

4. Current status of PVT treatment in liver cirrhosis

At this stage, the clinical treatment of patients with cirrhotic PVT requires a comprehensive assessment of multidimensional factors such as symptoms, PVT staging, lesion severity, and the occurrence of complications [1],and the selection of therapeutic regimens, the timing of their implementation, and the development of specific measures should be based on an individualized assessment. In current clinical practice guidelines, intervention strategies for PVT in cirrhosis are mainly categorized into (1) anticoagulation therapy, which inhibits the progression of thrombus through pharmacologic intervention; (2) thrombolytic therapy, which promotes thrombus dissolution by pharmacologic or mechanical means; and (3) Transjugular Intrahepatic Portosystemic Shunt (TIPS), in which a portal shunt is established. TIPS, which is used to relieve portal hypertension after establishing a portal shunt. The current indications for anticoagulation include (1) patients with acute exacerbations of PVT with significant symptoms, (2) patients with end-stage liver disease who are on the waiting list for liver transplantation, and (3) patients with complex disease complicated by mesenteric vein thrombosis. Thrombolytic therapy is mainly limited to some patients with PVT in the acute phase with significant symptoms, and the safety of this therapy needs to be further verified by more studies, while TIPS is mostly used in patients with cirrhotic PVT who have responded to or failed to respond to conventional anticoagulation therapy.

In the clinical management of PVT in cirrhosis, anticoagulation has been established as one of the key interventions, and this applied strategy needs to follow the principle of individualized treatment and is highly compatible with the recommendations of current authoritative guidelines [1]. According to the recommendations of the Baveno VII Portal Hypertension Consensus Update [11]the scope of anticoagulation may include (1) patients with recent occlusion or >50% occlusion of the main stem thrombus, with or without superior mesenteric vein involvement; (2) patients with clinically significant symptoms of PVT, regardless of the extent of thrombus extension and stage of the lesion; (3) patients with end-stage liver disease who are on the waiting list for liver transplantation, regardless of the status and extent of the thrombus occlusion; and (4) patients with <50% main stem thrombus obstruction who require initiation of anticoagulation if the lesion progresses or involves the superior mesenteric vein during 1 to 3 months of follow-up. Although some patients with PVT with mild symptoms can achieve self-healing, early anticoagulation is necessary after thrombus detection with regular monitoring and examination, not only to inhibit the re-expansion of thrombus scope, promote thrombus dissolution and vascular recanalization, but also essential for the patient's own organism's prognosis in the later stage. Valeriani et al [12]found that patients with PVT in cirrhosis had a significantly higher recanalization rate and slower thrombotic progression after anticoagulant therapy compared with cirrhotic patients without anticoagulant therapy. In a meta-analysis of multiple studies [3] it was concluded that anticoagulation was effective in improving PVT recanalization, slowing down the progression of thrombus without causing an increase in the overall risk of bleeding, and also had a positive effect on the survival of patients[13-14]. Therefore, early, timely and long-term anticoagulation therapy has an important impact on the recovery and prognosis of PVT patients.

In clinical practice, anticoagulant drugs are categorized into two main groups based on their mechanism of action and characteristics, traditional anticoagulant drugs and DOACs. Traditional

anticoagulant drugs include ordinary heparin, low molecular heparins (LMWHs), and Vitamin K antagonist (VKA) warfarin, etc., which have been widely used in clinical practice. However, the limitations of traditional anticoagulant drugs are gradually emerging with the deepening of clinical research and experimental evidence. The use of ordinary heparin requires the monitoring of activated partial thromboplastin time (APTT) to assess its anticoagulant effect, and it may cause thrombocytopenia and other adverse reactions. In contrast, LMWHs do not require specific monitoring, and are often used for rapid anticoagulation in patients with acute PVT, but the risk of heparin-induced thrombocytopenia should be cautioned against. In addition, the use of LMWHs in patients with renal insufficiency is limited, and the need for prolonged subcutaneous injections may result in lower patient compliance during treatment. Warfarin, as a classical oral anticoagulant, requires strict monitoring of INR and precise control of drug dosage, and is susceptible to food and multiple drug interactions during metabolism, leading to fluctuations in anticoagulant effects. For patients with cirrhosis, when hepatic coagulation factor synthesis is impaired, an increase in baseline levels of INR is often seen in the terminal stage of the disease. Therefore, how to establish an effective INR monitoring mechanism for warfarin anticoagulation in patients with liver disease and maintain it within a stable therapeutic window remains an urgent challenge in current clinical practice[15].

In recent years, DOACs have demonstrated significant advantages[16]： their pharmacokinetic and pharmacodynamic properties are relatively stable, eliminating the need for long-term monitoring; they are easy to administer, have a rapid onset of action, and are cleared from the body relatively quickly after cessation of drug use. In a meta-analysis [17],researchers compared the safety of DOACs with that of conventional anticoagulants in the treatment of PVT in cirrhosis and showed that the use of DOACs did not significantly increase the risk of drug-induced hepatic injury when compared with conventional anticoagulants. The use of DOACs in the treatment of PVT in cirrhosis is increasing, and their safety and efficacy in cirrhosis have been confirmed by guidelines and consensus, and they are also included as one of the drugs for anticoagulation therapy in various guidelines and consensus [1,10,18-19],but the specific regimen of anticoagulation therapy with DOCAs in patients with cirrhotic PVT has not been explicitly proposed. At this stage, the DOACs' mainly cover the inhibitors directly acting on factor Xa (such as rivaroxaban and apixaban) and those directly targeting factor IIa (such as dabigatran), among which rivaroxaban has been widely used in the patient population of cirrhotic PVT due to its good efficacy and safety,and has accumulated abundant clinical research data.In this article, we will focus on the application of rivaroxaban in the treatment of cirrhotic PVT, and systematically summarize and analyze it.

5. Efficacy and safety of rivaroxaban in the treatment of PVT in cirrhosis of the liver

Rivaroxaban, as a direct factor Xa inhibitor, has a mechanism of action that does not depend on the involvement of cofactors. The drug exerts its anticoagulant effect by specifically inhibiting the activity of free thrombin, FXa, and thrombinogenase, and ultimately acts on the endogenous and exogenous pathways of the coagulation cascade without directly affecting the level of pre-existing prothrombin [15,20].

Although DOACs have been categorized as anticoagulant therapeutic agents, there is still a lack of a comprehensive and clear definition of their efficacy in the treatment of PVT in cirrhosis, which makes it difficult to use them as the sole criterion for evaluating the efficacy of anticoagulation. In clinical practice, the efficacy of anticoagulation should be judged by taking into account different reactivity indexes, including but not limited to the recanalization rate of portal vein thrombosis, the rate of disease progression and the probability of recurrence, etc [15].Guo et al [21]established a rat model with both cirrhosis and intra- and extra-hepatic thrombosis by using portal vein ligation and CCl4 intoxication for 10 weeks and found that, after 6 weeks of rivaroxaban treatment, the efficacy

of anticoagulation in cirrhotic PVT was improved in a rat model with cirrhosis. After 6 weeks of treatment with rivaroxaban, it was found that coagulation was improved, portal blood flow velocity was increased, and thrombus was attenuated in cirrhotic PVT rats. This result once again demonstrates the usefulness of rivaroxaban in the treatment of cirrhotic PVT. Feng et al [22]performed PVT prevention in patients with cirrhosis after splenectomy, and compared the therapeutic effects of rivaroxaban in the observation group and aspirin combined with dipyridamole in the control group on the postoperative patients, and found that the portal vein diameter of the observation group was smaller than that of the control group, and the maximal and mean blood flow velocities were higher than that of the control group, at the same time, the incidence rate of PVT in the observation group was lower when compared with that of the control group, and this result indicates that rivaroxaban can effectively prevent the generation of PVT in patients with cirrhosis after splenectomy with a high degree of safety. This result suggests that rivaroxaban can effectively prevent and control the generation of PVT after splenectomy in patients with cirrhosis, and at the same time, the safety is high.He et al [23]retrospectively analyzed the efficacy of rivaroxaban in patients with PVT in cirrhosis, and the results showed that through the treatment of rivaroxaban, the liver function of the patients was improved, while the total bilirubin level was reduced, and there was a tendency of prolongation of blood zymogen time.LV et al [24]in a prospective observational study of anticoagulation and TIPS treatment of cirrhotic portal vein thrombosis, demonstrated that long-term anticoagulation with enoxaparin sodium or administration of rivaroxaban, instead of warfarin, was associated with reduced thrombosis and improved survival, and that neither regimen increased the risk of bleeding.

Rivaroxaban is mainly cleared by hepatic metabolic pathways in the body, so it can be a suitable treatment option for patients with liver function in Child-Pugh class A. For patients with liver function in Child-Pugh class B or C, the risks and benefits of the drug need to be further weighed when using it [1]. Data from some studies have shown [25-26]hat in the cirrhotic patient population, the safety of DOACs is not significantly different from that of conventional anticoagulants, and the risk of bleeding is also similar to that of conventional anticoagulants. It is worth noting that patients with cirrhosis are generally at risk of bleeding associated with coagulation abnormalities and portal hypertension, which requires clinicians to take into account individual differences and potential risks when formulating therapeutic regimens [27].In a retrospective study [28],it was found that long-term treatment with DOACs in patients with decompensated cirrhosis was often accompanied by a significant bleeding tendency and a high discontinuation rate, but no deaths due to bleeding events have been observed after medical intervention. Given the significant increase in the incidence of PVT in patients with decompensated cirrhosis, and the relative lack of clinical data on the use of DOACs for the treatment of PVT in these patients [29],the use of DOACs in patients with PVT in decompensated cirrhosis should be subjected to a rigorous, dynamic and systematic evaluation of its efficacy and safety. The use of rivaroxaban in clinical practice has similar characteristics. Studies [30]have shown that both rivaroxaban and dabigatran do not increase the risk of hemorrhage, provide a degree of safety, and improve liver function in patients. A retrospective study [31]showed that there was no significant difference in the incidence of hemorrhage between DOACs and warfarin in a group of cirrhotic patients, and suggested that the sample size of subsequent studies should be enlarged to include patients with cirrhosis in the Child-Pugh class C, so as to further validate the safety and effectiveness of the drugs. A study on the efficacy and safety of rivaroxaban application in patients with PVT in decompensated cirrhosis [32]showed that the drug exhibited a higher safety profile when low-dose rivaroxaban was used to treat patients with PVT in decompensated cirrhosis, and no significant hemorrhagic or hepatic impairment events were observed during treatment. Zhang et al [33]found that in 24 patients with Child-Pugh class B cirrhosis PVT treated with rivaroxaban, two bleeding events, one hematoma formation and one renal impairment occurred in the treatment group, with an

incidence of adverse events of 17%, indicating that rivaroxaban treatment does not increase the incidence of adverse events in patients with Child-Pugh class B cirrhosis combined with PVT in patients with Child-Pugh B cirrhosis combined with PVT, and the overall safety profile was favorable. Hum et al [34]included 45 patients with cirrhosis, 27 patients received anticoagulation therapy with DOACs, and the remaining 18 were anticoagulated with VKA or LMWHs. Statistical results showed that there was no significant difference in the overall rate of hemorrhagic adverse events between the two groups, but the rate of major hemorrhagic events in the DOACs group was significantly lower than that in the conventional anticoagulation group, and this result further demonstrated that the safety of DOACs can be ensured during anticoagulation therapy in cirrhotic patients. Although a large number of existing studies have confirmed the high safety profile of rivaroxaban in anticoagulation therapy, the occurrence of potential adverse reactions, such as bleeding, requires continuous attention in clinical application due to the heterogeneity of performance between individual patients in terms of differences in physiological function and severity of disease.

6. Timing and prevention of PVT anticoagulation in cirrhosis

In the clinical management of cirrhosis complicated by portal vein thrombosis, early diagnosis combined with early anticoagulation (time to thrombosis <6 months) is considered a key prognostic factor for predicting the outcome of thrombotic recanalization [35],but the time of formation of PVT in cirrhosis is often accompanied by uncertainty, and the process of diagnosis of the disease is often episodic, so it is recommended that the strategy of anticoagulant intervention should be implemented as early as possible in the clinic after the diagnosis of PVT is confirmed. Guidelines [1] suggest that the initial treatment cycle should be at least 6 months after the initiation of the anticoagulation program. For patients who achieve complete recanalization of the portal vein, this anticoagulation regimen can continue to be maintained, and the anticoagulation treatment cycle should be prolonged after comprehensive evaluation for special populations such as those waiting for liver transplantation, and those with a history of previous intestinal ischemia or intestinal necrosis. It is worth noting that although anticoagulation therapy can promote portal vein recanalization, studies have shown that the recurrence rate of thrombus is as high as 38%, there is a risk of thrombus re-formation, and the risk of recurrence is concentrated in the early stage after the termination of anticoagulation therapy, which is mainly related to the mechanism of thrombus re-formation [36].Therefore, after completing the anticoagulation therapy and achieving the expected efficacy, it can be considered to strengthen the thrombus recurrence prevention effect by appropriately prolonging the anticoagulation therapy cycle. During this process, continuous dynamic monitoring of portal hemodynamic status is recommended, focusing on the stability of revascularization quality.

A randomized controlled trial[37]suggested that prophylactic application of rivaroxaban after splenectomy combined with peripancreatic vascular dissections in cirrhotic patients significantly reduces the risk of PVT compared to low molecular heparin combined with warfarin regimen, while providing more optimal regulation of liver function indexes and coagulation mechanisms. However, another study [38]found that a patient with chronic atrial fibrillation combined with Child-Pugh class B cirrhosis developed PVT despite receiving 20 mg of rivaroxaban daily, which suggests that the conventional dose of rivaroxaban is not effective in preventing the formation of PVT in this particular patient group. Thus, although the anticoagulant effect of rivaroxaban is undisputed, there is a lack of high-quality clinical studies to confirm whether it can prevent the occurrence of PVT in cirrhosis [27].Therefore, when anticoagulant therapy is implemented, it is necessary to set up a standardized monitoring system to dynamically track the evolution of PVT and to closely prevent the occurrence of bleeding events through cyclic imaging evaluation and endoscopic screening.

7. Summary

Patients with cirrhosis are at a significantly higher risk of developing PVT compared with the general population, so accurate identification of this high-risk group is critical for the development of preventive intervention strategies. However, there is a lack of effective predictive models for the risk of PVT in cirrhosis in current clinical practice, and clinicians mostly rely on periodic imaging for early diagnosis and assessment of disease progression, which may lead to the inability to establish the optimal anticoagulation regimen in a timely manner, thus increasing the risk of thrombosis and hemorrhagic complications. Therefore, the optimization of monitoring protocols and the construction of accurate prediction models are of great clinical value in guiding individualized anticoagulation therapy and reducing the incidence of adverse events.

Most of the current clinical evidence on rivaroxaban anticoagulation for portal vein thrombosis (PVT) in cirrhosis comes from retrospective studies that have tentatively demonstrated the effectiveness of rivaroxaban in the management of PVT in cirrhosis, but clinical recommendations continue to suggest the need to adequately assess the risk of gastrointestinal bleeding after diagnosis and to initiate rivaroxaban anticoagulation as early as possible, when conditions permit, to improve PVT re rate and optimize patient prognosis. As a drug in the class of DOACs, rivaroxaban, by virtue of its precise efficacy and convenient administration, has given physicians and patients greater confidence and its potential for future application is more worthy of expectation. However, the efficacy and safety of rivaroxaban in cirrhotic PVT, especially in Child-Pugh class B/C patients, still need to be verified by more high-quality studies, and key issues such as the optimal dosing regimen, treatment cycle, and dose-adjustment strategy of rivaroxaban in the management of cirrhotic PVT need to be clarified and standardized in the further exploration in the future.

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