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Direct Oral Anticoagulant administration in cirrhotic patients with portal vein thrombosis: What is the evidence?

Portal vein thrombosis

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Abstract

In recent years, the traditional concept that cirrhosis-related coagulopathy is an acquired bleeding disorder has evolved. Currently, it is known that in cirrhotic patients, the hemostatic system is rebalanced, which involves coagulation factors, fibrinolysis and platelets. These alterations disrupt homeostasis, skewing it toward a procoagulant state, which can lead to thromboembolic manifestations, especially when hemodynamic and endothelial factors co-occur, such as in the portal vein system in cirrhosis. Portal vein thrombosis is a common complication of advanced liver cirrhosis that negatively affects the course of liver disease, prognosis of cirrhotic patients and success of liver transplantation. It is still debated whether portal vein thrombosis is the cause or the consequence of worsening liver function. Anticoagulant therapy is the mainstay treatment for acute symptomatic portal vein thrombosis. In chronic portal vein thrombosis, the role of anticoagulant therapy is still unclear. Traditional anticoagulants, vitamin K antagonists and low-molecular-weight heparin are standard-of-care treatments for portal vein thrombosis. In the last ten years, direct oral anticoagulants have been approved for the prophylaxis and treatment of many thromboembolic-related diseases, but evidence on their use in cirrhotic patients is very limited. The aim of this review was to summarize the evidence about the safety and effectiveness of direct oral anticoagulants for treating portal vein thrombosis in cirrhotic patients.

Key Words: Dabigatran; Rivaroxaban; Apixaban; Edoxaban; Bleeding

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Core Tip: The role of anticoagulant therapy in portal vein thrombosis is still unclear, especially in partial, chronic and asymptomatic thrombosis. Vitamin K antagonists and low-molecular-weight heparin were demonstrated to be safe and effective, with a

positive influence on liver function, portal hypertension and mortality. Direct oral anticoagulants are a new approach to treat portal vein thrombosis in patients with cirrhosis and have many advantages compared to classic anticoagulants, although evidence is still limited. In patients awaiting liver transplantation, dabigatran may be promising for preventing thrombosis progression because of the low rate of hepatotoxicity, predominant renal metabolism and reversibility in perioperative management.

INTRODUCTION

PORTAL VEIN THROMBOSIS

Definitions

Portal vein thrombosis (PVT) is defined as the presence of a thrombus within the portal vein, either in the main trunk or intrahepatic branches, which can extend to the splenic or superior mesenteric vein (SMV). Based on the degree of obstruction, PVT can be characterized as occlusive or nonocclusive. Based on onset, PVT can be classified as acute or chronic. Acute PVT includes a symptomatic onset and the exclusion of portoportal collaterals with imaging, while chronic PVT is defined as previously diagnosed PVT or as PVT associated with long-lasting signs of thrombosis such as cavernoma. A temporal cutoff dividing acute and chronic DVT has not been defined[1,2].

Prevalence and incidence

The heterogeneity of PVT incidence and prevalence is related to multiple factors, among the most important of which are cirrhosis severity, the clinical presentation of PVT and diagnostic techniques used to identify PVT. The analysis of a large multicenter study, which included 1243 cirrhotic patients with Child-Pugh A (863) or B (380), showed that the cumulative PVT incidence was 4.6%, 8.2% and 10.7% at the 1-, 3- and 5-year follow-up, respectively[3]. However, in advanced cirrhosis, the annual incidence was higher and ranged from 10% to 15%[1].

In the "Portal vein thrombosis Relevance On Liver cirrhosis: Italian Venous thrombotic Events Registry" (PRO-LIVER) prospective multicenter study, the PVT prevalence in

753 cirrhotic patients who underwent Doppler ultrasound was 17%, and Child-Pugh B or C, hepatocellular carcinoma (HCC), previous PVT and gastrointestinal bleeding were independently associated with PVT, suggesting that there was a correlation between the progression of disease and PVT[4]. Interestingly, in this study, 45 patients who developed PVT received anticoagulant therapy. According to Zhang *et al*, the prevalence was higher in advanced cirrhosis with acute decompensation than in compensated cirrhosis (9.36% vs. 5.24%)[5]. Acute PVT seems to be more common than chronic PVT in cirrhosis[6]. This is likely related to the clinical presentation of acute PVT vs. chronic PVT.

In the setting of liver transplantation, the prevalence of PVT ranges from 2% to 26%[7]. Francoz *et al* described a prevalence of 8.4% at the time of listing for transplantation and an annual incidence of 3.2% in patients without PVT at the time of listing[8]. In another retrospective study on approximately 400 Liver transplant candidates, the prevalence of PVT was 10.3%, of which 25% had PVT at the time of listing for transplantation, 17.5% developed PVT while waiting for transplantation and 57.5% were diagnosed with PVT during surgery[9].

Pathophysiology and risk factors for PVT

In noncirrhotic patients, PVT is uncommon and can occur more frequently in association with inherited or acquired thrombophilia. Major risk factors for PVT in noncirrhotic patients are myeloproliferative disorders, prothrombin gene G20210A mutation and antiphospholipid syndrome[10].

In cirrhotic patients, multiple systemic and local factors contribute to an increased risk of PVT. Recent evidence changed the traditional understanding that cirrhotic patients acquired bleeding disorders due to reduced levels of procoagulant factors. In chronic liver disease, the fragile rebalance of the hemostatic system involves coagulation factors, platelets and fibrinolysis. Regarding the coagulation system, a parallel modification of both prohemostatic and antihemostatic factors takes place. Antithrombin and protein C reductions [11,12] and factor VIII increases were shown[12], and low fibrinogen levels and low factor II, V, VII, IX, X and XI levels were demonstrated[12]. Concerning platelets,

thrombocytopenia due to sequestration, a shortened half-life and reduced production[13] may shift the balance toward bleeding. Instead, high levels of von Willebrand factor (vWF) and reductions in its cleavage factor, ADAMTS 13[14], promote thrombosis. Finally, the fibrinolytic system is rebalanced, with some alterations, such as low plasmin inhibitor levels promoting fibrinolysis, and other alterations, such as low plasminogen contrast fibrinolysis[14]. In liver cirrhosis, fibrinogen production is relatively unchanged, but functional fibrinogen levels are reduced. This functional defect is called acquired dysfibrinogenemia and is caused by the inadequate removal of excess sialic acid residues from fibrinogen, resulting in fibrin polymerization impairment[15,16]. How is procoagulant imbalance in this setting possible? In 2011, Tripodi *et al* demonstrated that protein C reduction (caused by reduced liver synthetic activity) and factor VIII increases (caused by vWF increases), which binds and protects factor VIII and reduces low-density lipoprotein-related protein and triggers resistance to thrombomodulin activity, which is one of the most important anticoagulant factors[17]. Thus, it is not surprising that a decrease in protein C (PC) causes an increase in factor VIII (FVIII) levels, and the FVIII/PC ratio predicts unfavorable outcomes in cirrhotic patients[18]. However, recent developments in this field suggest that in reality, coagulopathy in cirrhotic patients is much more complicated than previously thought (as described by the classic view), and classic tests used to determine this state are inaccurate. Therefore, new tools to detect cirrhosis-related coagulopathy, which consider antithrombin, protein C and FVIII, are needed. One of the most promising tests is the thrombin generation assay[19].

Hemodynamic factors play an important role in PVT development. A decrease in portal vein blood flow velocity of less than 15 cm/second is closely related to PVT development in liver cirrhosis[20–22]. Considering this, all conditions that reduce the velocity of portal flow can promote PVT development, such as nonselective beta blockers (NSBBs) or the presence of portosystemic shunts. NSBBs reduce the portal pressure gradient by decreasing cardiac output and inducing unopposed alpha-1 adrenergic-mediated splanchnic vasoconstriction, and they are widely used for the

primary and secondary prophylaxis of variceal bleeding[23,24]. A recent meta-analysis showed that NSBBs significantly increased PVT risk in cirrhosis. In this study, the authors suggest ultrasound follow-up to estimate portal vein blood flow in patients treated with long-term NSBBs[25]. Portosystemic shunts open when portal pressure increases to deviate the portal flow to the inferior vena cava through various collateral circles. The convergence of portal blood flow into these vessels, called the "steal effect", slows the portal flow velocity and is associated with a major risk of PVT, as found by Maruyama *et al*[26].

Inherited thrombophilic disorders, such as prothrombin gene G20210A polymorphisms[27], deficiencies of antithrombin, protein C and protein S, factor V Leiden[28], or lupus anticoagulant[29], increase PVT risk in patients with cirrhosis[30], but the low prevalence of these conditions does not justify screening to search for these alterations[31,32]. Other risk factors were associated with PVT in cirrhosis. Some evidence has demonstrated that the presence of endothelial damage predisposes patients to thrombosis[33]. This damage could be related to higher intestinal permeability and higher gut-derived bacterial lipopolysaccharide (LPS)[34], which also stimulate endothelial cells to produce and release factor VIII[35].

Intrabdominal surgery, especially splenectomy, significantly affects the development of PVT[5]. The etiology of liver disease may be associated with major PVT risk, such as nonalcoholic fatty liver disease (NAFLD)[21] or with a lower risk of PVT in cases of alcoholic cirrhosis, which might be correlated with the effect of alcohol on coagulant function and vitamin status[36].

Sarin *et al* proposed a model to assess the pretest probability of PVT. It is based on major criteria, such as Child-Pugh B or C, PVT history and presence of prothrombotic risk mutations, and minor criteria, such as new onset or worsening of portal hypertension, reduction in portal flow velocity < 15 cm/second, evidence of portosystemic shunt, active HCC, history of VTE, recent abdominal intervention, and acute abdominal clinical manifestations. The presence of 2 major, 1 major and 2 minor, or the presence of 4 minor criteria, suggests a high risk for PVT development[37]. This

score could help clinicians understand which patient could benefit from anticoagulant prophylaxis, but prospective trials are needed to establish the score's predictive role.

Clinical manifestations

The clinical presentation of PVT depends mainly on two factors: the extent of thrombotic occlusion, partial or complete, and the time of thrombus formation, acute or chronic.

Acute PVT typically presents with gastrointestinal symptoms (due to splanchnic congestion), such as abdominal pain, nausea and vomiting, up to severe gastrointestinal complications, such as bleeding, sepsis and lactic acidosis[38]. Splenomegaly is frequent, ascites is rare[39]. The symptoms can be more severe and prognosis unfavorable in cases of complete mesenteric thrombosis[6].

Chronic PVT is often asymptomatic and is usually accidentally discovered during radiological examinations performed for other reasons[40,41]. The clinical presentation of chronic PVT is related to manifestations of portal hypertension, such as ascites, hepatic encephalopathy, gastroesophageal variceal bleeding[6] and hypersplenism with pancytopenia[39]. In addition, neovessel formation and cavernomatosis can alter the anatomy of biliary ducts. The effects of these alterations can manifest with portal cholangiopathy, characterized by pruritus, obstructive jaundice and cholangitis, or "pseudocholangiocarcinoma", a tangle of neovessels mimicking cholangiocarcinoma cancer[39].

Diagnosis and staging of PVT

Doppler ultrasound is the most common diagnostic technique for PVT, with high sensitivity and specificity[40]. Generally, diagnosis with ultrasound occurs during screening for HCC in asymptomatic patients but should be performed in patients with suggestive symptoms[42] or in patients with deteriorating hepatic decompensation[1]. Normal PV flow excludes PVT, while positive results need further evaluations with second-level imaging techniques, such as CT or MRI, to confirm the presence of acute or chronic PVT[22], to exclude the presence of a neoplastic thrombus and to examine thrombus extension. Sherman *et al* proposed a scoring system called A-VENA, which

considers venous expansion, thrombus enhancement, neovascularity, tumors adjacent to the thrombus and alpha-fetoprotein levels to distinguish a tumor thrombus from a nonneoplastic thrombus in HCC patients being evaluated for liver transplantation[43]. A recent review and meta-analysis investigated the diagnostic value of contrast-enhanced ultrasound (CEUS) to differentiate PVT from neoplastic invasion in HCC. It was demonstrated that CEUS has excellent accuracy and could be considered a valid alternative to second-level imaging techniques[44]. In some cases, it is necessary to perform a histological exam of the thrombus to distinguish a nontumor thrombus from HCC vascular invasion. In this cases, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) represents a feasible and safe tool for selected patients as an alternative to classic transabdominal ultrasound-guided fine-needle aspiration[45]. Despite the use of multiple imaging techniques, PVT diagnosis can occur during surgery for liver transplantation. In the retrospective study conducted by Bert *et al*, incidental PVT diagnoses during surgery occurred in more than half of the PVT cases in the entire cohort[9].

The staging of PVT extension is very important to select treatments and to predict the potential response to treatment. However, a comprehensive classification of PVT does not exist. In the setting of liver transplantation, Yerdel's classification[46] divided PVT into four categories based on the degree of main portal vein obstruction and proximal and distal SMV extension. Each stage correlates with a different portal reconstruction approach, and for stages 2–4, with a lower graft survival. In 2016, Sarin *et al* proposed a new anatomico-functional classification of PVT in cirrhosis, which considers the site and extension of the thrombus, obstruction degree, duration and presentation, and functional relevance of the thrombosis; the aim of this classification is to allow for standardization in future research in this field[37].

Natural history and prognosis

The evolution of untreated PVT is still unclear. Three possible scenarios exist: spontaneous resolution, stabilization, or progression of the thrombus. Data regarding the occurrence of these possibilities are highly variable[22]. Spontaneous resolution or

stabilization of the thrombus is the most frequent evolution of PVT and occurs in 45% to 70% of cases[41]. Currently, data on the predictive factors for PVT progression are still lacking. Evidence suggests that the degree of occlusion and extension of the PVT do not correlate with the evolution of thrombosis[47]. Regarding prognosis, PVT seems to be related to a worse prognosis and to negatively influence the decompensation of cirrhosis and long-term survival[48]. Amitrano *et al* showed that PVT is associated with increased overall mortality risk in cirrhosis[27]. The same result was described in more recent studies, which reported that PVT is associated not only with an increased mortality risk[5,49] but also with a major incidence of ascites[49] and major variceal bleeding risks[5]. It is still unclear whether PVT is the cause or the consequence of liver deterioration, and the data are controversial because PVT is clearly associated with more severe portal hypertension and advanced cirrhosis[3]. Conversely, in compensated cirrhosis, the development of PVT is independent of liver disease progression and is not related to decompensation or lower OLT-free survival[50]. These findings might be explained by the fact that the population considered in these studies included a majority of patients with Child-Pugh A, who have fewer risk factors for PVT and a reduced mortality rate than patients with advanced cirrhosis. Regarding patients who are candidates for orthotopic liver transplantation (OLT), PVT can be detected at the time of listing for liver transplantation or can be diagnosed while patients are on the waiting list. The presence of PVT at the time of listing is associated with worse posttransplant survival[51] and with graft failure after OLT[52]. Although PVT is not a major contraindication for liver transplantation, the presence of a thrombus can reduce surgical feasibility, which is associated with a poor prognosis when nonphysiological reconstruction is performed[53,54]. When end-to-end anastomosis is performed, the survival rate at 1 and 5 years is similar between patients with or without PVT[55]. Conversely, the risk of portal vein rethrombosis, gastrointestinal bleeding and small bowel obstruction is higher when nonphysiological anastomosis is performed[56].

PVT is also associated with a prolonged duration of transplantation surgery (especially

when incidentally discovered at the time of surgery), prolonged hospitalization after surgery, and lower 1-year survival, which is independent of the time of detection[9]. The negative impact of PVT on post-OLT survival was documented by a recent meta-analysis, which reported significantly higher 30-day and 1-year mortality in patients with pre-OLT complete PVT than in those with partial PVT or without PVT[57]. The presence of PVT before transplantation is a risk factor for PVT recurrence after liver transplantation[7]. The onset of PVT after liver transplantation is associated with reduced graft and patient survival[58].

ANTICOAGULANT THERAPY IN PVT WITH CIRRHOSIS

Anticoagulant agents are the mainstay of therapy in many cases of thromboembolism, such as for the treatment of lower limb venous thrombosis, pulmonary embolism, or stroke prevention in atrial fibrillation.

The role of anticoagulants in cirrhotic patients with portal vein thrombosis is still unclear, especially in chronic asymptomatic PVT and in nonliver transplant candidates. Current guidelines do not propose definitive evidence-based treatment strategies for cirrhotic patients affected by portal vein thrombosis. The American Association for the Study of Liver Diseases (AASLD) suggests that the indication for treatment, anticoagulant type and duration of therapy should be considered on a case-by-case basis[59]. The European Association for the Study of the Liver (EASL) recommends starting anticoagulation with low-molecular-weight heparin (LMWH) in the absence of major contraindications for anticoagulant therapy, switching to vitamin K antagonist (VKA) treatment for at least 6 mo and ensuring that there is prior adequate prophylaxis for gastrointestinal bleeding. No indications were provided for the use of direct oral anticoagulants in this setting[2,59].

The classic anticoagulants commonly used in PVT in cirrhotic patients are LMWH and VKAs, which each has advantages and limitations. LMWH does not require monitoring and has an effect for a limited time. However, subcutaneous injection may reduce compliance, and low antithrombin III levels in cirrhotic patients may compromise the LMWH mechanism of action.

VKAs are usually used for long-term anticoagulation. Their advantages are oral administration and reversibility with vitamin K supplementation. Conversely, VKAs require INR monitoring (which is altered in patients with cirrhosis and probably does not reflect the real hemostatic status) and induce a decrease in anticoagulant proteins C and S, which are already reduced in cirrhotic patients. Fondaparinux, an indirect factor X-activated inhibitor, seems to be effective and safe in advanced cirrhosis, but very little evidence is available[60].

Efficacy and safety of classic anticoagulants in PVT with cirrhosis

A body of evidence suggests that anticoagulant treatment of PVT in cirrhosis is effective and safe. In a recent meta-analysis that included 1696 cirrhotic patients with PVT, anticoagulation therapy was significantly associated with portal vein recanalization, a decrease in PVT progression, and an improvement in survival, especially when treatment was started early[61]. According to these results, other recent systematic reviews and meta-analyses reported a pooled response rate to anticoagulation therapy that was considerably higher than that of the control group (66.7% vs. 26%)[62]. Recanalization of the portal vein in patients treated with anticoagulants is associated with decreased portal hypertension and related complications, with higher OLT-free survival[63].

Instead, the discontinuation of therapy in patients with previous PVT, which is itself considered a risk factor for recurrence[47], is associated with a high PVT recurrence risk[64] (rethrombosis rate of 46.7%) after stopping anticoagulation[61]. Therefore, the duration of anticoagulation after portal vein recanalization is controversial. Regarding safety, anticoagulant therapy in cirrhotic PVT is not associated with a significant increase in bleeding risk compared with that in untreated cirrhotic patients[62-64].

Regarding the incidence of bleeding, Mohan *et al* reported a pooled rate of bleeding that was similar in patients treated with anticoagulant and the corresponding controls (7.8% vs. 15.4%)[62]. Upper gastrointestinal bleeding in patients with cirrhosis on anticoagulation has the same severity and mortality as in patients with cirrhosis

without anticoagulation treatment[65]. In support of these findings, Wang *et al* demonstrated that anticoagulation did not influence overall bleeding and is, therefore, not a predictive factor for bleeding events[61].

In cirrhotic patients who are candidates for liver transplantation and are affected by PVT, the goal of anticoagulant therapy is to prevent PVT progression and to promote portal and superior mesenteric vein recanalization, allowing end-to-end anastomosis, which is associated with better outcomes. Available guidelines support the use of anticoagulant treatment in cirrhotic patients with PVT who are candidates for transplantation[2,59]; a recent study demonstrated a trend toward recanalization and a beneficial trend toward 1-year survival in cirrhotic patients with PVT awaiting LT who were treated with anticoagulant therapy[9]. No consensus exists regarding anticoagulation therapy after LT. A short course of anticoagulant therapy should be administered to reduce the risk of rethrombosis, while prolonged therapy should be recommended when nonphysiological reconstruction of portal anastomosis is performed[66].

As Ponziani *et al* suggested, the best recommendation for the future is to avoid PVT-related complications by identifying patients at a high risk for PVT and introducing prevention strategies and adequate prophylaxis[39]. In this field, only one prospective study demonstrated that prophylactic anticoagulation with LMWH in Child-Pugh B or C was associated with decreased hepatic decompensation and better survival[67]. Gaballa *et al* proposed a scoring system to predict and stratify the risk of PVT in cirrhosis. This score, called the PVT risk index (PVT-RI), was developed to predict the incidence of PVT in liver transplant candidates and considers five variables associated with a higher PVT risk: age, African American descent, the Model for End-Stage Liver Disease (MELD) score, moderate/severe ascites and nonalcoholic steatohepatitis (NASH). A PVT-RI < 2.6 has a negative predictive value of 94% and could be used to establish the time of ultrasound surveillance. A PVT-RI > 4.6, with a positive predictive value of 85%, could identify a high-risk population that would benefit from anticoagulant prophylaxis[68].

In this review, neoplastic PVT, which occurs as a complication of HCC, was not considered since anticoagulation therapy is not recommended. Instead, the treatment of choice for neoplastic PVT includes surgical resection, radiotherapy, TACE and systemic therapy[69]. Nonneoplastic PVT occurs in approximately a quarter of patients with HCC, but no evidence exists about the role of anticoagulants in this setting[47].

Direct oral anticoagulants (DOACs)

In the last ten years, direct oral anticoagulants (DOACs) have been increasingly prescribed to prevent stroke in nonvalvular atrial fibrillation and to treat thromboembolic disorders, such as venous thromboembolism and pulmonary embolism, after their approval[69,70].

In regard to pharmacodynamic properties, DOACs can be divided into two categories: factor X-activated inhibitors, such as rivaroxaban, apixaban and edoxaban, and factor II-activated inhibitors, such as dabigatran. Compared with classic anticoagulant molecules (LWMHs and VKAs), among the advantages of DOACs are their oral administration in fixed doses, poor interaction with other drugs and predictable pharmacokinetic profiles and anticoagulant effects; therefore, they do not need laboratory monitoring. Rivaroxaban is metabolized by cytochrome P450 without forming active metabolites and is mostly eliminated by renal excretion. Apixaban and edoxaban are metabolized by cytochrome P3A4 without forming active metabolites. Apixaban is eliminated by renal excretion (~25% of the absorbed dose) and hepatic metabolism but mainly by intestinal excretion (~55%). Edoxaban is eliminated by the hepatobiliary (~65%) and renal (~35%) systems. Rivaroxaban, apixaban and edoxaban act independently of endogenous antithrombin. This could be useful in cirrhosis where antithrombin is reduced. Dabigatran is an oral prodrug metabolized by esterase in various organs, including the liver, but not by hepatic cytochrome, and approximately 80% of it is eliminated by renal excretion[71]. Renal impairment is the main factor that influences the pharmacokinetics of DOACs. Regarding hepatic function, clinical recommendations or contraindications are based on a small amount of evidence because cirrhotic patients have usually been excluded from trials of these drugs[47]. Experience from the long-term

use of DOACs in this setting is still limited. All DOACs can be used in patients with mild hepatic dysfunction (Child-Pugh A) without a significant bleeding risk. In patients with moderate hepatic dysfunction (Child-Pugh B), dabigatran, apixaban and edoxaban can be used with caution, while rivaroxaban should not be used because of increased plasma concentrations and pharmacodynamic effects[72]. In severe hepatic dysfunction (Child-Pugh C), DOACs are not recommended[73].

Regarding hepatotoxicity, a recent systematic literature review reported two new cases of hepatocellular liver injury in patients treated with rivaroxaban[74], in addition to a case report by Liakoni *et al*[75], who described his experience with ximelagatran, which was withdrawn two years after approval because of severe hepatotoxicity[76]. However, the real hepatotoxic effect of new oral anticoagulants is still unknown. All new oral anticoagulants can lead to hepatotoxicity with an idiosyncratic mechanism, but this adverse event is very rare[77]. A recent meta-analysis considering patients treated with DOACs demonstrated that the incidence of drug-induced liver injury (DILI) was insignificant when the data of each drug were individually analysed[78]. A prospective study showed that dabigatran, rivaroxaban, apixaban and edoxaban are associated with a lower incidence of liver injury than warfarin, and among these, dabigatran seems to be the safest[79], probably due to its pharmacokinetic characteristics.

When the EASL published guidelines about PVT treatment in cirrhosis in 2016, no specific indications were described for the use of DOACs, and they emphasized the need for randomized trials to assess the efficacy and safety of DOACs in cirrhosis[2]. These recommendations have been confirmed by the most recent AASLD guidelines. The lack of evidence is the result of patients with signs of liver disease being excluded from clinical trials with DOACs[59].

Safety of DOACs in cirrhosis: current evidence

Evidence regarding the safety of DOACs in cirrhotic patients affected by atrial fibrillation or venous thromboembolism suggests that DOACs may be safe in patients with mild to moderate chronic liver disease, with rates of bleeding similar to those of traditional anticoagulants[80]. In a recent publication, Violi *et al* concluded that DOACs

may be considered for the treatment of deep venous thrombosis or for prophylaxis in patients with atrial fibrillation when cirrhotic patients are not eligible for VKAs[47]. In a more recent extended systematic review and meta-analysis, Menichelli *et al* investigated the safety of DOACs compared to VKAs in patients with advanced liver disease who received anticoagulants for atrial fibrillation or deep vein thrombosis. The primary endpoints were any bleeding, major bleeding, gastrointestinal bleeding, and intracranial hemorrhage. Considering more than forty thousand patients, the authors concluded that treatment with DOACs compared to VKAs is associated with a lower risk of major bleeding, intracranial hemorrhage, and all types of bleeding (pooled hazard ratios 0.39, 0.48 and 0.73, respectively), with no difference in gastrointestinal bleeding. Subsequently, the subanalysis of only cirrhotic patients showed no difference in safety outcomes between the DOAC and VKA groups[81]. In accordance with this study, a retrospective longitudinal analysis conducted by Serper *et al* also demonstrated that DOACs were associated with a significantly lower incidence of bleeding than VKAs in a cohort of cirrhotic patients with atrial fibrillation. Moreover, both anticoagulant classes have been proven to be capable of reducing all-cause mortality and the incidence rate of hepatic decompensation when compared with any anticoagulant therapy[82].

Regarding the safety of DOACs in cirrhotic patients with PVT, one of the first studies was conducted by De Gottardi *et al*, who compared the rate of bleeding in cirrhotic patients with that in noncirrhotic controls. In this study, 36 patients affected by mild to moderate liver cirrhosis treated with DOACs for a mean of 9.6 mo were included. Major or minor bleeding was reported in 5 cirrhotic patients (13.9%); however, in 58 noncirrhotic patients treated with DOACs, minor and major bleeding was reported in 9 (15.9%) patients [83].

Regarding the safety of DOACs compared to traditional anticoagulants, Intagliata *et al* reported a comparable bleeding rate in patients affected by mild to moderate cirrhosis. In this study, the rate of bleeding was analyzed in 20 cirrhotic patients prophylactically or therapeutically treated with rivaroxaban or apixaban compared with 19 cirrhotic

patients treated with traditional anticoagulants. The indications for anticoagulant therapy were atrial fibrillation or VTE, including PVT. The total bleeding and major bleeding rates were not significantly different between the two groups[84]. Similarly, Hum *et al* investigated the difference in bleeding events between DOACs and traditional anticoagulants in cirrhotic patients. Twenty-seven patients treated with rivaroxaban or apixaban and 18 patients treated with warfarin or LMWH affected by atrial fibrillation and venous thromboembolism, including PVT, were included. Total bleeding was similar in the two groups: 10 events in the traditional group and 8 in the DOAC group (P = 0.12). Major bleeding was significantly higher in the traditional group than in the DOAC group (5 vs. 1, P = 0.03)[85]. Table 1 summarizes the evidence about DOAC safety in cirrhosis. The main limitation in assessing DOAC safety in patients with cirrhosis is the lack of uniformity in outcome definitions. In the studies examined, different bleeding definitions were used. To address this lack of uniformity, Nisly *et al* conducted a systematic review and meta-analysis considering only studies in which the primary safety outcome was major bleeding according to the definition of the International Society on Thrombosis and Haemostasis (ISTH). In these studies, pooled analysis demonstrated the absence of a statistically significant difference between DOACs and traditional anticoagulants for ISTH major bleeding in cirrhotic patients treated for stroke prevention or venous thromboembolism[86].

Efficacy of DOACs in PVT: current evidence

Studies regarding the efficacy of DOACs to treat PVT in cirrhosis are very limited (Table 2). Ai *et al* studied the efficacy of rivaroxaban and dabigatran [87]. In this prospective study, 80 patients with chronic PVT were enrolled and divided into two groups: 40 patients were treated for 6 mo with DOACs, 26 patients with rivaroxaban 20 mg once daily, 14 patients with dabigatran 150 mg twice daily, and 40 control patients were not treated with anticoagulant therapy. At 0, 3 and 6 mo, patients were tested with ultrasound and pulsed Doppler to establish the portal blood flow rate and CT portal angiography to examine thrombus extension. Regarding efficacy, in treated patients, a

significant response in terms of complete/partial recanalization and improved portal blood flow velocity compared with the control group was demonstrated, which was superior at 6 mo than at 3 mo. The majority of recanalized patients were Child-Pugh A, and none of them were Child-Pugh C. Regarding safety, no significantly different bleeding rates in the treated *vs* the control group were shown. In this study, patients with moderate to severe esophageal varices and platelet counts below 50x10^9/L were excluded.

Comparing DOACs with classic anticoagulants, Hanafy *et al* designed a randomized, controlled, interventional study in which they compared the efficacy and safety of rivaroxaban with warfarin to treat acute portal thrombosis in HCV-related cirrhosis. Eighty patients were enrolled. After 3 days of enoxaparin 1 mg/kg every 12 h, forty patients continued therapy with rivaroxaban 10 mg twice daily; instead, controls were treated with warfarin at variable dosages to maintain the international normalized ratio (INR) between 2 and 2.5. Regarding efficacy, the primary outcome was partial or complete PVT recanalization; the secondary outcome was the absence of recurrence after the end of therapy. Regarding safety, the main outcome was major bleeding. The results showed that rivaroxaban was more effective than warfarin in terms of complete or partial recanalization, time to recanalization, recurrence of PVT and safety, with a significantly lower risk of major bleeding[88].

In a retrospective analysis, Nagaoki *et al* evaluated the efficacy and safety of edoxaban compared with warfarin to treat PVT in cirrhotic patients after 2 wk of danaparoid sodium. Twenty patients were enrolled in the edoxaban group and received 60 mg or 30 mg once daily depending on renal function, body weight and concomitant drug administration. Thirty patients were enrolled in the control group treated with warfarin, and the INR target was 1.5–2. The duration of the study was 6 mo. Efficacy was evaluated in terms of PVT volume and PVT reduction rate at 2 wk and 1, 3 and 6 mo, as assessed with dynamic CT. Safety was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Additionally, in this study, the findings demonstrated the effectiveness of DOACs compared to warfarin,

showing a significant reduction in thrombus volume after 6 mo of treatment and a higher prevalence of complete response. Regarding safety, there were no significant dissimilarities between the two groups[89].

AREAS OF UNCERTAINTY

Although evidence has shown the noninferiority of DOACs compared with traditional anticoagulant therapy, the studies examined varied in design, and no universal outcome definition was used. Furthermore, in these studies, no uniformity in dosage strategy, treatment duration, clear predictor efficacy or evidence on the ideal time of initiation and duration of anticoagulant therapy were described. This poses a challenge for establishing the real effect and benefit of anticoagulant therapy with DOACs in terms of portal recanalization.

Regarding safety, the definition of bleeding events varied between studies. However, the safety of DOACs appears comparable or superior to that of classic anticoagulants. In addition, a major limitation, which is shared in these studies, regards the characteristics of the patients included. Most of the patients considered were affected by compensated cirrhosis. Insufficient data are reported about the safety and efficacy of DOACs in patients affected by advanced liver cirrhosis.

No evidence exists about the role of prophylactic anticoagulant therapy. Villa *et al* demonstrated that prophylactic anticoagulant therapy with LMWH has some beneficial effects on the deterioration of liver function and survival. Most likely, DOACs may contribute to reducing liver damage, especially in early cirrhosis stages, and superior drug tolerance makes them suitable for wider use. The pharmacodynamic and pharmacokinetic characteristics of DOACs could be an important tool for portal vein thrombosis prophylaxis, but patients who would benefit most from this therapy have not yet been identified. A defined stratification of the portal vein thrombosis risk is still lacking. There is a need to validate scores to establish PVT risk and subsequent prophylactic anticoagulant therapy.

In the setting of liver transplantation, anticoagulant therapy with DOACs in patients with PVT on a waiting list is a potential option to allow recanalization of the portal vein

and to allow physiological reconstruction of vessels. The major advantage for patients who are waiting for liver transplantation is the possibility of counteracting the anticoagulant effect with reversal agents at any time, such as idarucizumab for dabigatran or andexanet alfa for rivaroxaban. The main limitations are the high cost, availability, and lack of evidence about their use in cirrhotic patients, especially with decompensated disease.

CONCLUSION

CONCLUSION AND PERSPECTIVES

This review emphasizes that DOACs could represent a valid alternative to the currently poorly defined standard of care for portal vein thrombosis. However, we show that the lack of evidence and inhomogeneity of studies regarding outcome definitions to evaluate efficacy and safety poses challenges to clinical trial design to evaluate DOACs and, as consequence, its use in clinical practice.

As shown here, in cirrhotic patients with mild hepatic function impairment, the safety and efficacy of new oral anticoagulants seems to be noninferior compared with classic anticoagulants, especially in patients with a low bleeding risk (platelet count >100,000/mm^3 and no high-risk esophageal varices). No significant differences between dabigatran, rivaroxaban, and edoxaban have been observed, while data on apixaban for treating portal vein thrombosis in cirrhotic patients are limited[90]. In patients with moderate liver dysfunction, anticoagulant drugs need to be selected with caution, especially those metabolized by liver cytochromes. Considering this, molecules with a predominantly renal metabolism might be preferred in more advanced liver disease. In patients awaiting liver transplantation, dabigatran may be promising in preventing thrombosis progression because of the low rate of hepatotoxicity, predominant renal metabolism and reversibility by idarucizumab in perioperative management. Well-designed randomized controlled trials are needed to further evaluate the safety and efficacy of DOACs to treat PVT in cirrhotic patients, especially in patients listed in the OLT setting.

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