Portal vein thrombosis in cirrhosis: Why a well-known complication is still matter of debate

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Abstract

Portal vein thrombosis (PVT) represents a well-known complication during the natural course of liver cirrhosis (LC), ranging from asymptomatic cases to life-threating conditions related to portal hypertension and hepatic decompensation. Portal flow stasis, complex acquired hypercoagulable disorders and exogenous factors leading to endothelial dysfunction have emerged as key factors for PVT development. However, PVT occurrence remains unpredictable and many issues regarding its natural history, prognostic significance and treatment are still elusive. In particular although spontaneous resolution or disease stability occur in most cases of PVT, factors predisposing to disease progression or recurrence after spontaneous recanalization are not clarified as yet. Moreover, PVT impact on LC outcome is still debated, as PVT may represent itself a consequence of liver fibrosis and hepatic dysfunction progression. Anticoagulation and transjugular intrahepatic portosystemic shunt are considered safe and effective in this setting and are recommended in selected cases, even if the safer therapeutic option and the optimal therapy duration are still unknown. Nevertheless, their impact on mortality rates should be addressed more extensively. In this review we present the most debated questions regarding PVT, whose answers should come from prospective cohort studies and large sample-size randomized trials.

Key words: Portal vein thrombosis; Liver cirrhosis; Hypercoagulability; Anticoagulation; Direct oral anticoagulants

Core tip: Portal vein thrombosis (PVT) represents a common and potential life-threating complication of liver cirrhosis. Anticoagulant therapy is advised in selected cases, in particular for liver transplant candidates. Despite the advanced knowledge in PVT

pathogenesis and diagnosis, many issues regarding its natural history and prognostic outcome remain elusive. Likewise, the safer anticoagulant option, the potential role of direct oral anticoagulants and the optimal duration of therapy are still matter of debate. Given the clinical significance of this pathological entity, these cardinal issues should urgently be addressed in large prospective cohort studies and randomized trails.

INTRODUCTION

Portal vein thrombosis (PVT) refers to blood clot formation within the trunk of the portal vein (PV) or its main branches, which may extend to the splenic and superior mesenteric veins (SMV). It can range from a partial and asymptomatic obstruction of the vessel to a complete blockade of portal venous blood flow, leading to hepatic decompensation, variceal bleeding and intestinal infarction secondary to portal hypertension (PH). PVT represents a well-known complication during the natural history of liver cirrhosis (LC), as a result of portal flow stasis, inherited or acquired prothrombotic disorders and/or vascular endothelial injury due to abdominal infection, surgery or trauma[1,2].

It occurs mainly in advanced stages of LC and in the presence of hepatocellular carcinoma (HCC). It is worth mentioning that cirrhotic patients with HCC may experience 2 types of PVT: "non-malignant" PVT, secondary to hemostatic disturbances superimposed by HCC, and "malignant" PVT, due to direct invasion of the PV by neoplastic cells. Since "malignant" PVT represents an established exclusion criteria for liver transplantation (LT), surgical resection and imaging-guided HCC treatments, early recognition of this entity is crucial for prognosis definition and decisions making[3].

Although PVT in LC was first described almost 150 years ago and it has been widely studied in clinical and experimental studies, many issues regarding its pathogenesis, natural history, prevention and treatment are still matter of debate[4]. Which are the predisposing factors? What is the natural evolution of asymptomatic cases? Is PVT clinically significant on LC natural history or does it represent an epiphenomenon of advanced liver disease? What is the impact on patient outcome including those undergoing LT? Which patients should be treated and how long? Which anticoagulant could represent a safe therapeutic option? How long should therapy be extended in case of repermeation, give the risk of thrombosis recurrence? How much should anticoagulation (AC) be prolonged before considering therapy to have failed? This review aims to summarise the current knowledge on "non-malignant" PVT occurring in the setting of LC, with a focus on the aforementioned unanswered questions.

EPIDEMIOLOGY

PVT was first described in 1868 in a 20 years-old man, presenting with ascites, splenomegaly and esophageal varices (EV)[4]. Since then PVT in LC has been increasingly recognized due to amelioration of diagnostic imaging methods and better awareness amongst clinicians.

The relative risk of developing PVT in the presence of LC is increased more than 7-fold above the risk observed in the general population[5]. In particular PVT prevalence increases with the degree of liver failure and in the setting of HCC, being as low as 1% in patients with compensated disease and rising to 8%-25% in candidates for LT and 40% in the presence of HCC[6,7]. Cirrhosis aetiology may also play a role in PVT development. Emerging data suggest that non-alcoholic steatohepatitis (NASH) may be an independent risk factor for significant thrombotic events, including PVT, in patients with decompensated cirrhosis[8,9]. Different diagnostic methods used in various studies may be responsible for prevalence data heterogeneity, which ranges from 0.6% to 16% in angiography or surgery studies to 10%-25% in ultrasound (US)

studies[6]. Incidence of PVT in LC has been investigated in a limited number of reports. Values of 7.4% and 16% per year have been reported in small sample size studies involving patients with severe cirrhosis or listed for LT, respectively. One of the largest study performed in 1234 patients with compensated cirrhosis [Child-Turcotte-Pugh (CTP) A or B] reported a cumulative incidence of PVT of 4.6%, 8.2% and 10.7% at 1, 3 and 5 years, respectively[10,11].

However, the retrospective design of most studies, the small sample size and the risk of underestimation of asymptomatic cases, do not allow definitive conclusions to be drawn. Recently, the multicenter prospective study PRO-LIVER (PVT relevance on LC: Italian venous thrombotic events registry), including 753 Caucasian cirrhotic patients (50% outpatient, 50% with mild severity disease), reported a prevalence of US-documented PVT of 17% (43% asymptomatic cases) and an annual incidence rate of 6.05%. Such incidence resulted much higher in patients with a history of PVT (18.9 per 100 patient-years *vs* 4.1 per 100 patient-years in those without prior PVT at admission) indicating that PVT per se carries a risk for recurrences[12,13].

PATHOPHYSIOLOGY

Venous stasis, hypercoagulability and endothelial dysfunction, summarized in the "Virchow triad", are the 3 known pathophysiologic factors predisposing to thromboembolic events, including PVT. PV stasis secondary to liver architectural derangement is thought to play the main role in the setting of LC. We have found that a portal flow velocity lower than 15 cm/s at Doppler US is the most influential risk factor for PVT development in LC and our data were confirmed by another case-control study[11,14]. PV stasis may also be the result of a spontaneous portosystemic shunt causing a "steal" syndrome. In the study of Maruyama *et al*[15] the presence of collateral vessels with a flow volume of more than 400 mL/min and a flow velocity of more than 10 cm/s resulted a significant predictive factor for the occurrence of PVT in virus-induced cirrhosis. Since non-selective beta blockers (NSBB) act reducing PV inflow velocity and are extensively used for primary and secondary prevention of EV bleeding in LC, several studies have investigated their potential contribution to PVT development reporting conflicting results. No association between PVT and NSBBs treatment was reported by Violi *et al*[12], which confirmed a significant increase in PVT prevalence among patients with CTP class B and C, HCC, history of upper gastrointestinal bleeding or PVT, and older age. Conversely EV and NSBBs exposure resulted risk factors for PVT occurrence in other studies[16,17]. Although these results are in appearance conflicting, taken together they may suggest that the primary culprit of PVT may be the significant PH associated with more advanced liver disease which lead to NSBBs prescription, instead of NSBBs use per se. Future trials addressing the use of NSBBs in cirrhotic patients should include development of PVT as a specific safety outcome to allow definitive conclusions and comparisons between different types of NSBBs.

Based on the presence of thrombocytopenia and prolongation of conventional coagulation tests, cirrhotic patients were traditionally considered "auto-anticoagulated". However a growing body of clinical and laboratoristic evidence allowed to dispel this old dogma, showing a complete reassessment between pro- and anti-hemostatic drivers in LC (Table 1), potentially leading to a hypercoagulation state, which is not expressed by routine coagulation tests[1,7,18]. This hypothesis is supported by the evidence that thrombin generation in LC is normal or even increased compared to healthy subjects notwithstanding prothrombin time and activated partial thromboplastin time are prolonged[19,20]. Likewise, the reduction of platelet (PLT) number seems counterbalanced by PLT hyperractivity, as assessed by increased urinary excretion of 11-deydro-thromboxane B2 and by consistent elevation of p-selectin expression on PLT surface at rest and after thrombin stimulation and higher serum beta-thromboglobulin and platelet factor-4 alpha compared to controls[21,22]. It has been proposed that changes in PLT-von Willebrand factor (vWF) interaction, which is one of the first step of PLT adhesion, might compensate defects in PLT number and function. Higher molecular weight multimers of vWF have been extensively described in LC, as a result of reduced vWF cleaving protease ADAMTS-13, and seem to play a pivotal role in increasing PLT thrombogenic potential[23]. Although low serum ADAMTS-13 levels and activity were significantly associated with PVT development in cirrhotic patients irrespective of CTP and Model for end-stage liver disease (MELD) scores, further studies are needed to determine whether these parameters could be used in everyday clinical practice to predict PVT occurrence in LC[24,25].

Concurrent thrombophilic conditions have been reported in 5.6% of patients with

Table 1 Reassessment between anti- and pro-hemostatic drivers in liver cirrhosis

Hemostasis phase	Anti-hemostatic drivers	Pro-hemostatic drivers
Primary hemostasis (vasoconstriction and platelet plug formation)	Thrombocytopenia	Platelet hyperactivity High molecular weight multimers von Willebrand factor levels Low ADAM TS 13 levels and activity
Secondary hemostasis (coagulation cascades)	Low anticoagulant factors levels: AT, protein C and S High procoagulant factor levels: factor VIII	Low procoagulant factors levels: fibrinogen, factor II, V, VII, IX, X, XI
Tertiary hemostasis (fibrinolysis)	Low plasminogen and high PAI levels	High t-PA levels Low TAFI and plasmin inhibitor levels

AT: Antithrombin; ADAM TS 13: A disintegrin-like and metalloproteinase with thrombospondin type 1 motif 13; PAI: Plasminogen activator inhibitor; t-PA: Tissue plasminogen activator; TAFI: Thrombin-activatable fibrinolysis inhibitor[18].

PVT and LC, however their contribution to PVT development is difficult to assess since they may be a secondary phenomenon of parenchymal liver disease rather than a primary disturbance[7]. Among different thrombophilic genetic defects, G20210A prothrombin gene variant has been the most common abnormality associated with PVT in patients with LC with a prevalence of 21.4%-29% and an odds ratio of 5.9 for development of PVT[26,27]. Another study demonstrated that a relevant proportion of cirrhotic patients with PVT harbours a myeloproliferative disorders secondary to JAK2 V617F mutation[28]. Other hypercoagulable risk factors may occur in patients with LC, but none results as definitive risk factor for PVT development[28,29].

Furthermore, many poorly understood exogenous factors may act in the background of the above-mentioned prothrombic causes, tipping the balance towards thrombotic or bleeding complications. ''Low-grade'' endotoxemia, as a result of bacterial translocation from intestinal lumen to the portal circulation in advanced stage of LC, has been proposed as potential trigger of clotting system. Lipopolysaccharide derived from gut microbiota has been shown to increase endothelial release of factor VIII[30]. However, despite a clear correlation between endotoxemia and a marker of thrombin generation in LC, a study on 49 cirrhotic patients failed to demonstrate a correlation between both endotoxemia and platelet activity with PVT occurrence[31,32]. Anyway, the potential role of endotoxemia as prothrombotic trigger in the portal circulation of cirrhotic patients remains attractive and should be addressed more extensively in larger studies before drawing definitive conclusions. Among different LC etiologies, NASH is emerging as a potential risk factor for PVT, as it is associated with increased plasminogen activator inhibitor and reduced protein C levels[9]. If these findings will find confirmation, PVT occurrence might increase in the near future since NASH is becoming the leading cause of LC.

Endoscopic therapy of bleeding EV (sclerotherapy and variceal band ligation), abdominal surgery, inflammation or trauma and vascular invasion by neoplastic cells (HCC, cholangiocarcinoma, hepatic metastasis) have been all proposed as potential determinants of PVT, due to direct vascular injury and disturbance of blood flow. PVT has been described in 16% of cirrhotic patients (70% with concomitant thrombophilic conditions) undergoing endoscopic therapy for EV after a mean follow-up period of 16 mo[26]. Opposite results were obtained by another prospective study performed in cirrhotic patients undergoing sclerotherapy for EV which failed to demonstrated an increased risk of PVT development[33]. Previous abdominal surgery and splenectomy have also been reported as risk factors for PVT. In particular splenectomy has been associated with a 10-fold increase in the risk of PVT development, independently of liver dysfunction severity, in a retrospective study involving 113 cirrhotic patients without malignancy[29,34,35].

PVT PREDICTION

The role of serum markers for PVT prediction in patients with LC remains elusive. A recent meta-analysis suggested that cirrhotic patients with PVT might have higher D-dimer concentrations than those without PVT and that postoperative D-dimer testing is worthwhile for the diagnosis of PVT after PH-related surgery. However, significant heterogeneity among studies limits generalizable conclusions[36]. Protein C and S levels have also been tested as potential predictor of PVT development without definite conclusions[11,37]. What is clear is that the true thrombotic potential in this group of patients is more complex than appreciated by measuring individual protein markers. Based on these evidence Sarin *et al* proposed a pre-test probability

assessment for PVT prediction based on 10 criteria, 3 major (CTP class B or C; prior history of resolved PVT; prothrombotic risk factors such as factor V Leiden mutation, prothrombin gene mutation, MTHFR mutation) and 7 minor (evidence of a large portosystemic shunt or large isolated gastric varices; HCC; previous/or active systemic venous thrombotic events or abortions; acute abdomen; new onset or worsening PH complications; recent endoscopic, radiological or surgical abdominal interventions; portal flow velocity < 15 cm/s). Although attractive, this scoring system requires validation in prospective clinical studies[38].

DIAGNOSIS

In the majority of patients with cirrhosis, PVT is an incidental finding, during routine US, computed tomography or magnetic resonance imaging evaluation. In other cases diagnosis is made after a new event of hepatic decompensation or abdominal pain. The first-line technique for PVT detection is Doppler US, with sensitivity of about 90% for complete PVT and about 50% for partial PVT and high operator-dependence. Contrast-enhanced imaging techniques, including contrast-enhanced US, have comparable sensitivity for PVT diagnosis, allowing in addition a better definition of PVT extension as well as an evaluation of underlying malignancy and other sequelae[1,2,7]. HCC proximity to PVT, enlargement of the PV > 23 mm, enhancement of the thrombus in the arterial phase of contrast enhanced imaging scan or PV arterial-like flow on Doppler US have been proposed as reliable radiologic criteria for "malignant" PVT, confining histologic confirmation to selected uncertain cases[3]. After PVT diagnosis, upper gastrointestinal endoscopy is warranted to assess the presence and degree of EV.

PVT NATURAL HISTORY

PVT encompasses 2 different entities: acute PVT and chronic PVT (also called portal cavernoma). They represent successive stages of the same disease, since acute PVT may be followed by lysis of the thrombus or cavernous transformation of PV, consisting in porto-portal collaterals formation within or around the thrombosed vessel in an effort to bypass venous obstruction[1]. Changes related to cavernous transformation of PV have been described to occur already 6-20 d after acute PVT and are more common in patients without concomitant liver disease, since PV flow stasis in LC usually prevents collateral channel dilatation[39].

The most common evolution of acute PVT is spontaneous resolution or disease stability, which have been described from 45% to over 70% of cases in different studies[9,40,41]. However, data regarding predictors of PVT natural course are very scarce. In particular no significant association has been found between thrombus age and PVT degree at diagnosis and spontaneous PV recanalization[40,42]. Likewise age, sex, severity of liver and renal function, EV, previous PH-related bleeding, ascites, location of thrombosis and portal cavernoma were no significant predictors for PVT resolution in another retrospective study[43]. Only Maruyama *et al*. demonstrated that the diameter and flow volume in the largest collateral vessel at the time of diagnosis of PVT were negatively associated with spontaneous improvement of PVT, however these data require prospective external validation[15].

Recurrence of PVT after spontaneous recanalization has also been described in some cohort studies, ranging from 21.3% (19 of 89 patients, mean follow-up 47 mo) in the prospective cohort study by Nery *et al*[10] to 45% (9 of 20 patients, mean follow-up of 63.3 mo) in the retrospective study by Maruyama *et al*[10,15]. Considering the possibility of thrombus recurrence, the patients should continue to monitor the PV patency after spontaneous PV recanalization.

CLINICAL IMPACT ON CIRRHOSIS PROGRESSION AND OUTCOME

PVT occurrence is thought to have a negative impact on LC prognosis, because it produces a further increase in PH which may lead to potentially life-threatening bleeding events and worsening of liver function. However, contrary to common clinical belief, the actual prognostic value of PVT on liver disease progression and outcome remains an unsolved issue, since clinical studies are usually based on small cohorts of patients and short follow-up periods. D'Amico *et al*. prospectively reported

a more than 3-fold higher risk of failure to control active variceal bleeding in cirrhotic patients with PVT, irrespective of treatment modality (endoscopic hemostasis or surgical shunting), whereas in a subsequent retrospective analysis Dell'Era *et al*[44,45] showed that PVT was associated with longer time to EV eradication (8 d difference) but not with treatment failure. It has been proposed that the non-occlusive nature of most PVT cases involved in the second study and the improvement achieved in gastrointestinal bleeding management could explain these conflicting results. The impact of PVT on multiple LC outcomes has been investigated in a recent meta-analysis involving 2436 cirrhotic participants[46]. The study reported a significant association of PVT with both mortality and ascitic decompensation, but did not evaluated the pooled effect of PVT on other markers of hepatic decompensation such as gastroesophageal variceal bleeding or hepatic encephalopathy due to data insufficiency[46]. On the contrary, a recent prospective multicenter study on LC outcome did not find a prognostic role of PVT (mainly non-occlusive) on either mortality and hepatic decompensation[10]. It should be considered that the small number of studies evaluated and the lack of randomized controlled trials limit meta-analysis conclusions generalization. Similar results were obtained by Qi *et al*[47], that, after conducting a systematic review of the literature, concluded that heterogeneity in data reporting and lengths of follow-up among studies did not allow to draw conclusions about PVT consequences on LC outcomes.

Furthermore, it is worth mentioning that progression or regression of partial PVT seem to have no impact on LC natural history. In particular Luca *et al*[40] found that spontaneous improvement of PVT did not provide any benefit in terms of development of LC-related complications, LT and survival since CTP score at diagnosis was the only independent predictor of survival and hepatic decompensation on multivariate analysis. Based on these impressive findings, it has been speculated that PVT occurrence and LC progression may represent independent and synergistic phenomena resulting from the same pathophysiological mechanisms. In particular intrahepatic microvascular thrombosis secondary to hepatic necroinflammation may act as the key determinant of both diseases, leading to liver ischemia, cell death, loss of functioning hepatic mass and enhanced fibrogenesis, through a process, called "parenchymal extinction", which ultimately leads to liver dysfunction, PH worsening and PVT occurrence[18,48]. This hypothesis is supported by the results of Villa *et al*[49] who reported that daily prophylactic dose of low molecular weight heparin (LMWH) for 12 mo prevented hepatic decompensation and PVT development in patients with compensated cirrhosis (CPT B7-C10) and conferred a significant survival benefit in the 5-years follow-up. The same authors postulated that LMWH protective effect on the course of the liver disease was mediated by an improvement in intestinal microcirculation and reduction in bacterial translocation and liver inflammation rather than by PVT prevention. These findings although impressive were not confirmed by other studies[49].

CLINICAL IMPACT ON LT OUTCOME

PVT prevalence among candidates awaiting LT varies from 2.1% to 26%, being unrecognized pre-operatively in up to 50% of cases[50-52]. Historically PVT poses relevant challenges during LT-surgery due to increase in technical complexity, operative time, blood transfusion requirements and intensive care unit/hospital stays, which may all negatively affect outcomes. In the last decades, improvement in medical and surgical strategies allowed to overcome most of previous mentioned difficulties and, as a consequence, PVT is no longer considered an absolute contraindication for LT[53]. In a retrospective study involving 191 patients undergoing LT between 2005 and 2014, the presence of pre-transplant PVT did not affect significantly the need of blood components transfusion and surgery time (except for severe grades of PVT), but was associated with higher, even if not statistically significant, 30-d mortality[54].

To date the impact of PVT on morbidity and mortality after LT remains unclear, because the small number of published reports obtained controversial results and most of them did not differentiate between partial and occlusive PVT. According to the results of a recent metanalysis, the survival rates in this setting mainly depend on PVT type and surgical technique[50,51]. In particular, whereas incidentally discovered and partial PVT had a limited effect on post-LT outcomes, patients with complete PVT extending to distal superior SMV showed a lower 1-year survival rate with no impact on 5-year survival[50,51,55]. Furthermore, end-to-end PV anastomosis was associated with the same survival rates for patients with and without PVT regardless of its degree and extension, whereas non-anatomic portal anastomoses (cavoportal hemi-

transposition; renoportal anastomosis; PV arterialization) were characterized by a worse prognosis[56,57]. Based on these data, it has been proposed that high selected LT-candidates with porto-mesenteric thrombosis should be addressed to transplant centres with large specific experience in PVT evaluation and management[51,56]. Indeed surgeon ability to establish a physiological portal anastomosis to the graft seems the most important factor in predicting patient outcome.

The recurrence rate of PVT after LT has reduced from 36% in pioneering experiences to 2%-3% in recent years[53]. The rate of re-thrombosis has been ascribed to great degree and extension of pre-LT PVT, severe pre-LT PH and the need of PH-treatments, large portosystemic collaterals, mismatches in the size of the donor and the recipient PV, severe graft oedema, non-anatomical anastomosis, pediatric transplantation[58]. Post-LT PVT may significantly reduce both graft and patient survival and cause limitations or loss of future options for re-LT, particularly when these events occur intraoperatively or early after LT[59].

TREATMENT OPTIONS

Currently, robust data on the optimal management of PVT in the setting of LC are lacking and no definitive evidence-based recommendations have been reported in clinical guidelines or consensus conferences[1,2,7]. Available strategies include AC therapy and, in some technically suitable patients, transjugular intrahepatic portosystemic shunt (TIPS). If no treatment is started, a close imaging surveillance is advised, but the best time frame to perform US-screening is still not well defined. However as patients with cirrhosis should undergo screening US for HCC every 6 months, assessment of the PV can be performed simultaneously without significant additional cost and is recommended[7]. In case of patients on wait-list for LT, time frame might be shortened to 3 months given the aforementioned potential implications on LT outcome and surgical planning[58].

Anticoagulation

The utility of AC in patients awaiting LT is extensively shared. The rationale consists in achieving venous recanalization in case of thrombosis extending to the SMV or alternatively to prevent thrombus extension in the portal mesenteric junction, in order to allow conventional end-to-end PV anastomosis, which is associated with better outcomes in comparison with other surgical approaches[58,60]. In this setting AC leads to complete recanalization in about 40% of cases and should be prolonged until LT given the high rates of PVT recurrence after withdrawal[61,62]. No consensus exists concerning AC indication, dosage and duration after LT, however early post-operative AC with a short course of heparin is performed in many centres in high-risk liver recipients with an underlying prothrombotic state, especially in those undergoing "non-anatomical" procedures[56,63]. Conversely AC use for those patients who are not candidate to LT remains controversial, given the retrospective nature of most of the available data, the bleeding-related concerns and the heterogeneous rate of spontaneous recanalization, which makes it difficult to evaluate the real efficacy of different treatments. Experimental data suggest that AC my play an important role in patients with chronic liver disease, since it has been demonstrated that AC may prevent fibrogenesis through inhibition of fibrin and factor Xa in animal models[64,65].

According to the recent European Association for the Study of the Liver and American Association for the Study of Liver Diseases guidelines, AC treatment is advised for at least 3-6 months in the presence of cirrhotic-PVT and should be continued for some months after PV repermeation or until transplant in LT candidates, while it might be continued lifelong in case of SMV thrombosis and intestinal infarction[1,2]. A more prudent approach has been suggested by the 7th International Conference on Coagulation in Liver Disease, which recommends AC treatment for LT candidates with occlusive main PVT with or without proximal extension into the SMV and on a case by case basis and after multi-disciplinary discussion for high grade PVT in non-transplant population[7]. All guidelines underline the absolute need of gastroesophageal varices screening prior to AC therapy, in order to perform primary or secondary bleeding preventive strategies.

Although LMWH and vitamin K antagonists (VKA) are considered the first choice for PVT treatment unrelated to cirrhosis, their role in cirrhotic patients remains still unclear. LMWH is commonly used in the acute setting and has the advantage of a fixed dose without laboratory monitoring; however, daily subcutaneous injections may reduce compliance and low levels of antithrombin III together with reduced glomerular filtration rate due to hepato-renal syndrome may require unpredictable dose adjustments. A recent study compared different doses of enoxaparin (1.5 mg/kg

per 24 h *vs* 1 mg/kg per 12 h) for cirrhotic-PVT treatment showing comparable efficacy but a significantly higher rate of injection-site haemorrhage, epistaxis, or haematuria in the 1.5 mg/kg group[66]. VKAs are chosen for long-term AC but spontaneous INR prolongation and interference with MELD score make their use particularly challenging. Recently, the reduction of endogenous-thrombin-potential has shown reliability for AC monitoring in LC and may allow to overcome some of the above-mentioned limits in the near future[67]. Safety and efficacy issues of AC for cirrhotic-PVT treatment are still debated and have recently been addressed by 2 meta-analyses[68,69]. In the study of Qi X *et al*., involving 16 studies, LMWH and VKA were associated with acceptable major and minor bleeding rates (pooled rate 3.3%) and a relatively high rate of PV recanalization (pooled rate 66.6%, 41.5% for complete PV recanalization). However the inclusion of both comparative and non-comparative studies and the heterogeneity of outcome definitions does not allow to draw generalizable conclusions[68]. In the second meta-analysis performed on 8 studies with a total of 353 patients, PV recanalization was observed in 71% of patients treated with AC (*vs* 42% of untreated patients) with a complete recanalization rate of 53% (*vs* 33% of untreated patients). The same authors reported significantly lower rates of clot progression (9% *vs* 33%) in the AC group without differences in major or minor bleeding events between the 2 groups (11%)[69]. Although these results were encouraging, clinical and methodologic heterogeneity between studies, lack of prospective randomized studies and the inclusion of 2 studies involving patients undergoing invasive procedure for PH-treatment (TIPS placement and partial splenic embolization) suggest caution in clinical practice. To date, no clear predictors of efficacy have been established. In a recent prospective study involving 65 patients with PVT (72% non-occlusive) treated with LMWH, treatment efficacy was related to age of the thrombus and time interval (< 6 mo) between estimated thrombus onset and treatment start[70]. These results were consistent with a previous small report of Maruyama *et al*[71] who suggested that a positive intra-thrombus enhancement on CEUS, indicating a not completely organized thrombus, may be a potential indicator of successful recanalization in response to AC treatment.

This controversial issue is further complicated by the lack of data about the impact of PVT resolution on patient survival in most of studies. In a retrospective analysis of 63 cirrhotic patients with PVT, complete PV recanalization secondary to VKA treatment carried a significant reduction in long-term risk of PH-related complication and need for LT[72]. Likewise a recent retrospective study on 182 cirrhotic patients with mild liver disfunction (13% CTP C) and PVT, showed that LMWH or VKA therapy was associated with higher survival rates in comparison with untreated patients during a median follow-up of 19 mo[73]. Another retrospective cohort of 80 patients, mainly in CTP B/C stage, with non-tumoral PVT, reported no influence of AC treatment on overall LT-free survival but a beneficial effect on LT-free survival among those with MELD ≥ 15 compared to untreated patients[74].

Only one case-series study investigated the effect of fondaparinux 2.5 mg/day in acute PVT in 7 patients with decompensated LC. All patients were CTP class B–C, 6 with ascites and 2 with hepatic encephalopathy. The study showed that all patients had a recanalization of the PV after 7-21 d of treatment, and no side effects were reported[75].

Direct oral anticoagulants (DOACs), including direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), are attractive oral alternatives to VKA in many clinical settings. However, their role in cirrhotic patients is still unknown, since patients with remarkable liver disease have been excluded from most of the randomized clinical trials on DOACs. Indeed in this setting potential hepatotoxicity and unpredictable pharmacokinetics related to various degree of hepatic elimination (apixaban 75%, rivaroxaban 65%, edoxaban 50%, dabigatran 20%), cytochrome P450 and plasma protein binding levels alterations, overcame the advantages of no need of laboratory monitoring, rapid onset of action and oral formulation[76].

However increasing safety data coming from small clinical studies and in vitro analyses renewed interest on DOACs use in the presence of compensated hepatic impairment. In a retrospective study involving 39 cirrhotic patients (CTP A and B) receiving DOACs (rivaroxaban or apixaban) or traditional AC (VKA and LMWH), bleeding events did not differ significantly between study groups and no drug-induced liver injury was documented over a 3-year period[77]. These results were in concordance with those of a previous meta-analysis, which suggested no increased risk of drug-induced liver injury with DOACs compared to conventional AC[78]. Likewise another retrospective study, including 27 patients on DOACs (rivaroxaban or apixaban) and 18 on VKA/LMWH, mainly in the CTP B stage, reported similar total bleeding events and significantly less major bleeding episodes in the DOACs group[79]. It is noteworthy to mention that small sample sizes and the limited number

of CTP C patients restrict the applicability of these results in clinical practice and underline the need of larger prospective studies.

Also DOACs efficacy for PVT treatment remains controversial, since available data come from case reports and series, mainly referring to rivaroxaban and apixaban use in compensated cirrhotic patients (Table 2)[80-88]. Nagaoki *et al*[84] randomized 50 cirrhotic patients with variable CTP scores (29 A, 16 B, 5 C) and PVT to receive either VKA or edoxaban (dose adjusted to weight and creatinine clearance) for a total of 6 mo after 2 initial weeks of daparinoid sodium therapy. They reported a significantly higher PVT volume measured on CT in patients treated with VKA than in those receiving edoxaban and no significant differences regarding GI bleeding or other adverse effects among the 2 study arms. However the target INR of 1.5-2 in VKA group (inferior to the standard target of 2-3) and the absence of patients with CTP C in the group receiving edoxaban suggest caution when interpreting these results[84]. In addition a case report pointed out the efficacy of rivaroxaban in preventing PVT in LC, describing high-grade PVT occurrence in a 81 year-old woman with cryptogenic LC under treatment for chronic atrial fibrillation[85]. Based on current evidence and pending randomized controlled trials, it has been suggested that DOAC should be restricted to well compensated LC patients (CTP A and B) with platelet count > 50,000, after hematologic consultation[7].

Transjugular intrahepatic portosystemic shunt

TIPS allows to create a low-resistance channel for portal venous flow between the hepatic vein and intrahepatic portion of the PV, through an expandable metal or polytetrafluoroethylene covered stent. It finds wide applications in PH-related complication of LC, such as refractory or recurrent variceal bleeding and refractory ascites[89]. TIPS placement with mechanical and/or pharmacologic thrombolysis represents also an attractive treatment option for PVT when AC is contraindicated or fails, but technical success of the procedure decreases in the presence of extended thrombosis or cavernous transformation of PV, so its use in these settings have been long discouraged. Recent interventional advances, including trans-hepatic or trans-splenic route beyond the standard trans-jugular access and refinement of stents, have increased procedure efficacy allowing to face always more complex cases[90]. Therefore nowadays TIPS represents a suitable solution for selected patients with symptomatic complete main PV thrombosis and significant PH, with or without PV cavernous transformation, with reported rates of re-canalization ranging from 60% to 92% depending on the vascular access technique[7]. In a recent meta-analysis of 13 studies (399 patients, 92% cirrhotic) TIPS (alone or in combination with catheterdirected thrombolysis and/or thrombectomy) was feasible in 95% of cases, carried a moderate risk of major complications (10%, mainly when additional catheter directed thrombolysis was performed) and was highly effective in achieving sustained recanalization of PVT (81% of cirrhotic patients at 12 mo)[90]. In the evaluated studies PV re-thrombosis was not a frequent event after endovascular therapy and TIPS dysfunction was even less frequent, particularly with new covered stents. Noteworthy, the AC use post TIPS was associated with a non-significant higher pooled shunt patency rate (86% *vs* 83%), in accordance with previous studies[91,92]. These results are particularly attractive since TIPS alone, likely due to the high velocity flow created by the shunt, seems effective in maintaining long term PV patency, allowing to avoid AC treatment. Conversely SMV involvement, which has been associated with lower patency rate in many studies, might benefit from post-TIPS AC but further confirmations are required[90,91]. Moreover, TIPS placement resulted useful for PV revascularization as a bridge treatment to LT, and no association between shunt misplacement or occlusion and intra- or post-operative LT complication rates have been reported[93-96]. TIPS alone or in combination with percutaneous mechanical and/or pharmacologic thrombolysis resulted also safe and effective in selected cases of PVT post-LT not responsive to AC[97,98].

CONCLUSIONS

PVT is a common complication of LC, however its occurrence still remains elusive. More advanced stages of disease, previous history of PVT, concurrent thrombophilic genetic defects, venous stasis, HCC and recent endoscopic, radiological or surgical abdominal interventions have been proposed as the most reliable tools for PVT prediction, even if a pre-test scoring system is still lacking. Routine laboratory tests are unable to predict hemostatic balance in LC, while global coagulation assays, including thrombin generation tests and thromboelastography, although promising require validation in this clinical setting.

Table 2 Studies on direct oral anticoagulants efficacy and safety in cirrhotics with portal vein thrombosis

Ref.	Study design	No. of patients	Thrombosis extension	Drug and dosage	Duration (mo)	Outcome	Bleeding complication
Martinez *et al*[80]	Case report	1	Complete PVT+ SMVT	UFH (BT) + rivaroxaban 20 mg daily	6	Complete recanalization	No
Intagliata *et al*[81]	Case series	5	3 PVT, 2 PVT + SMVT	2 Rivaroxaban 20 mg daily (1 VKA as BT) 3 Apixaban 2.5 mg twice daily	1-7	Complete recanalization (2 treated with rivaroxaban) Stable (1 treated with apixaban) Unkown (2 other cases)	No
De Gottardi *et al*[82]	Prospective	22	N/A	Rivaroxaban/Dab igatran/ Apixaban (60% VKA or LMWH as BT) mainly at lower dose	14.6 (mean)	N/A 1 recurrence of PVT with rivaroxaban	1 major GI bleeding and 4 minor bleedings
Yang *et al*[83]	Case report	1	PVT	Rivaroxaban 15 mg twice daily for 3 wk, then 20 mg daily	6	Complete recanalization	No
Nagakoky *et al*[84]	Prospective	20	PVT	Edoxaban 30 mg daily (16) or 60 mg daily (4) (2 wk of danaparoid sodium as BT)	6	Partial recanalization	3 major GI bleedings
Ponziani *et al*[85]	Case report	1	PV and intrahepatic branches thrombosis	Already on rivaroxaban 20 mg daily treatment, then LMWH	N/A	Portal cavernoma	No
Lenz *et al*[86]	Case report	1	Partial PVT	Rivaroxaban 10 mg daily	5	Complete recanalization (recurrence after withdrawal)	No
Qi *et al*[87]	Case report	1	Occlusive SMVT SVT	Rivaroxaban 15 mg daily for 1 mo then 10 mg daily	3	Partial	Upper GI bleeding
Pannach *et al*[88]	Case report	1	PV and intrahepatic branches thrombosis	Rivaroxaban 20 mg daily	N/A	Resolution	No

UFH: Unfractionated heparin; VKA: Vitamin K antagonists; BT: Bridging therapy; LMWH: Low molecular weight heparin; PVT: Portal vein thrombosis; SMVT: Superior mesenteric vein thrombosis; SVT: Splenic vein thrombosis; GI: Gastrointestinal.

Currently, robust data on the optimal management of PVT in the setting of LC are lacking because of studies and patients heterogeneity. If no treatment is started, a close US-surveillance is advised, with a time frame of 6 mo in asymptomatic patients and 3 mo in patients on wait-list for LT. Furthermore, gastroesophageal varices screening is recommended prior to AC therapy for primary or secondary bleeding preventive strategies. AC is certainly required for patients awaiting LT, since it allows venous recanalization in case of thrombosis extending to the SMV or prevents thrombus extension to the portal mesenteric junction, which complicates surgical procedure and is associated with worse outcomes. AC in non-transplant population with high-grade PVT is more controversial, given the lack of benefit on LC outcomes, and should be established on a case by case basis.

LMWH and VKA are used for acute and long-term AC in LC, even if efficacy and safety data are not conclusive. DOACs use in LC population would be attractive but, pending randomized controlled trials, they should be restricted to well compensated patients after hematologic consultation. Interventional radiology, such as TIPS placement with mechanical and/or pharmacologic thrombolysis, represents also an attractive treatment option when AC is contraindicated or fails, but even if extended thrombosis or cavernous transformation of PV decrease technical success.

Certainly many advances regarding PVT pathophysiology, natural history and

treatment in LC have been made during the last decades. However, cardinal questions still remain unanswered. The answers to these questions should come from prospective cohort studies and randomized trials with large sample size, including detailed information about thrombus age, site and extension and a focus on short and long-term outcomes. Since these information could considerably change current clinical practice, the debate on PVT must go on.

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