Editorial

How to treat non-tumoral portal vein thrombosis in cirrhosis? Towards the use of direct-acting oral anticoagulants

Isabelle Ollivier-Hourmand[1], Aurélie Plessier[2,3,4,5]

[1]Service d'Hepatologie et de nutrition CHU Cotes de Nacre, Caen, France; [2]Service d'Hepatologie, Hôpital Beaujon, APHP, Clichy, France; [3]DHU Unity, Hopital Beaujon, APHP, Clichy, France; [4]Universite Paris Diderot, Sorbonne Paris Cite, Paris, France; [5]Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris, France

Correspondence to: Aurélie Plessier, MD, PhD. Service d'hepatologie, Hôpital Beaujon 100, boulevard du General Leclerc, Clichy 92110, France. Email: aurelie.plessier@aphp.fr.

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Nagaoki *et al.* suggest that edoxaban a direct-acting oral anticoagulant (DOAC) may be more effective than warfarin in case of chronic portal vein thrombosis (PVT) complicating cirrhosis (1). Furthermore, the conclusions of the study are that edoxaban following an initial therapy with danaparoid sodium, is effective to reduce the volume of thrombosis, without significantly increasing the risk of bleeding.

The presence of cirrhosis is associated with a relative risk of 7.3 of developing PVT in the general population. PVT is the most common thrombotic event occurring in cirrhotic patients, with a reported prevalence ranging from 2% to 23%. Complications of PVT may be an extension of thrombosis to the mesenteric vein, with intestinal infarction as a dreaded complication and may also jeopardize liver transplantation when extending to splenic and mesenteric vein. When treating with anticoagulation, [vitamin K antagonist (VKA) or low molecular weight heparin (LMWH)] recanalization rate ranged from 55% to 75% at a mean interval time of 6 months and overall bleeding complications were encountered in 5% of patients. Recommendations for anticoagulation in cirrhotic PVT are experts recommendations, all based on retrospective studies and none on blinded randomized controlled trials: EASL recommends anticoagulation after implementing an adequate prophylaxis for gastrointestinal bleeding at therapeutic dose for at least 6 months, or lifelong in patients candidates to liver transplantation, or with superior mesenteric vein thrombosis, or with a past history suggestive of intestinal ischemia (2). The first line treatment is usually a LMWH followed by VKAs. However, in patients with cirrhosis, anticoagulant dose adjustment is difficult to assess whatever the anticoagulant is administered and recommendations concerning monitoring of these drugs are scarce. First, the reliability of the anti-Xa assay to monitor LMWH is low due to the reduction of antithrombin, a typical feature in patients with advanced liver disease. Second, the prothrombin time is often prolonged because of spontaneous reduction of the clotting factors. The doses of VKAs usually necessary to reach the therapeutic target range may be lower (3-5). However there is currently no reliable data on the international normalized ratio (INR) target in cirrhotic patients in particular in patients with significant liver failure (e.g., factor V below 50%). EASL recommendations insist on the following point: INR target aims a therapeutic interval of 2.0–3.0, but the INR value might not be representative of the real anticoagulation and the results may vary between centers. Therefore, VKAs and LMWH have both a risk of under and over dose. DOACs unlike VKAs directly target clotting factors activated thrombin (dabigatran) or the factor Xa (rivaboxaban or apixaban, edoxaban) without the intermediary action of Antithrombin. However, the metabolism of DOACs is strongly modified in renal and hepatic failure, as well in case of denutrition, frequent in cirrhotic patients and difficult to assess (6-8).

One of the originality of this study is the initial use of danaparoid sodium, instead of LMWH. Danaparoid sodium is indicated for treatment of patients with an acute episode of heparin-induced thrombocytopenia (HIT), and for prophylaxis in patients with a history of HIT. Even though, a retrospective study showed that HIT was more frequent in patients with thrombosis of the hepatic veins (28.1% *vs.* 5.2%; P<0.0001) (9), there is no similar data on HIT in patients with PVT complicating cirrhosis. In this study, Nagaoki *et al.* observed a reduction of PVT volume in all patients at the 2nd week of treatment in the absence of hemorrhagic complication (1). Similar results were previously published from the same team: 26 cirrhotic patients with PVT were treated with 2-week administration of danaparoid sodium with a median reduction rate of PVT volume of 77% (range, 18–100%) with no hemorrhagic complication (10). However administration is intravenous or subcutaneous two times per day, it is contraindicated in severe hepatic failure, unlike LMWH there is no antidote, and there is additional cost compared to standard anticoagulation using these alternative anticoagulants. For all these reasons, routine prescription of danaparoid sodium in the absence of HIT is mainly limited to this Japan team. Thus randomized data is needed to assess a superiority of danaparoid sodium to standard anticoagulation in this context.

The main point of the study is to assess edoxaban efficacy on thrombosis recurrence rate at 6 months and edoxaban safety, compared to a group of patients treated with VKAs. DOACs have theoretical advantages over heparins or VKAs. The main advantage is that they don't require dose-adjustment by laboratory tests, thus the issue on the validity of the INR or anti Xa could not be problematic in this setting. Other theoretical advantages of the DOACs are their oral administration, not influenced by diet, their quick absorption effect with immediate anticoagulant effect and their short ten hours half-life elimination. However, cirrhotic patients have been deliberately excluded from phase III trials using DOACs, and there is only one European retrospective study, reporting DOACs efficacy and safety in splanchnic vein thrombosis in declared cases, with or without cirrhosis, and two series reporting efficacy and safety of DOACs compared to "traditional" anticoagulation therapy (LMWH or VKA) in either cardiac, deep vein thrombosis or PVT (1,6,11). Therefore, Nagaoki's study is the first study assessing the use of DOACS, in patients with PVT complicating cirrhosis, compared to VKAs only. Nevertheless, comparison is retrospective and not randomized. Even though, the groups seem comparable, patients in the edoxaban group have been carefully selected. Edoxaban is contraindicated in case of severe renal and liver failure; thus 50% of patients in VKA group are Child B or C *vs.* 25% in edoxaban group; even though it is not statistically significant. Severity of cirrhosis and extension of thrombosis are both known risk factors for PVT. Importantly, the doses of VKA used in the VKA group are much lower than the doses usually needed, as the INR target is 1.5–2 in the study, and at 6 months of treatment the INR target was achieved in only 57% of the patients. Therefore, the results showing significant higher recanalization rate with edoxaban vs VKA (P<0,001) from the Nagaoki's study, have to be cautiously interpreted (1). Nevertheless, the 70% rate of "complete response" (defined as complete disappearance of the PVT) in the group of patients treated with edoxaban, is close to the highest reported rates in the literature with other anticoagulants.

The most important results are that when doses are cautiously chosen, mainly adapted to renal failure, the risk of bleeding seems low, 15% at 6 months *vs.* 7% with VKAs, and easily controlled with endoscopic therapy. Thirty five percent of edoxaban is excreted by the kidney, and the rest is biliary and fecal. The dose of edoxaban was lowered to 30 mg in the majority of patients due to creatinine clearance of 30–50 mL/min or body weight ≤60 kg. In cirrhosis, risk factors identified for bleeding are platelets <50,000/mm^3, severity of portal hypertension and liver disease (12,13). It has recently been shown that factors that impact the outcome of upper GI bleeding in patients under anticoagulant therapy are degree of multiorgan failure and comorbidity, but not anticoagulant therapy itself (14).

Another major point is that no liver toxicity was encountered. Recently, a severe hepatitis was reported in two patients treated with rivaroxaban (15).

Although this study is supporting the fact that complications related to DOACs and efficacy on portal vein recanalization seem equivalent to traditional anticoagulation in cirrhosis, as suggested in other small series, data are still too scarce to conclude to the superiority of DOACs on traditional anticoagulation in cirrhosis. Pharmakocinetic data in the most severe patients and randomized comparative studies are still needed to answer these questions.

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