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Mini-review

Direct oral anticoagulants and cirrhosis: More evidence still needed for efficacy and safety in portal vein thrombosis

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In the context of cardiovascular diseases, venous thrombosis and its embolic clinical manifestations are the third most frequent cause of morbidity and mortality, closely associated with aging but also occurring in the young. Among the mechanistic factors, an important role is played by the physiologically slow flow of blood in the veins, but a heightened activity of the coagulation enzyme system is usually more relevant. The role of hypercoagulability is epitomized by the demonstrated efficacy of anticoagulant medications to prevent venous thrombosis in at risk people. Anticoagulants are also the mainstay of management of acute episodes of venous thromboembolism, being efficacious to prevent thrombus extension and embolization in the short term period and recurrence in the long term. While this approach to management is supported by solid evidence pertaining to venous thrombosis of the lower limbs (the most frequent site), the situation is uncertain when a thrombotic occlusion occurs in the portal and other splanchnic veins. Portal vein thrombosis (PVT) develops typically and more frequently in patients with cirrhosis, particularly in those with advanced disease awaiting orthotopic liver transplantation. PVT is a relatively frequent event, being reported in 20% up to 50% of patients with cirrhosis and being associated with a two-fold increased risk of mortality, particularly after liver transplantation [1-4].

With this background, it is surprising that clinical studies designed to evaluate the efficacy and safety of anticoagulation in the management of acute and chronic PVT in cirrhosis are scanty. Vitamin K antagonists (VKAs), used by Francoz et al. [5] in the frame of a prospective study including 22 patients, were associated with a 42% recanalization rate of the portal vein. However, the use of warfarin and other VKAs has not become widely employed in cirrhosis-associated PVT, for various reasons: the altered pharmacokinetics and pharmacodynamics of these drugs in advanced liver disease, the inadequacy of the International Normalized Ratio (INR) to monitor their dosage, as well as the fact that the plasma decrease of the naturally occurring anticoagulant proteins C and S induced by VKAs make warfarin a less than ideal choice in cirrhosis patients who have low baseline plasma levels of these moieties [6]. Two independent groups from Italy chose instead to use low molecular weight heparins (LWMH) as the anticoagulant of choice in such cases, and obtained rates of recanalization of the portal vein of 33% in 29 patients [7] and 36% in 35 patients [8], suggesting that anticoagulation with LMWHs is associated with a favorable rate of complete recanalization without evidence of an unacceptably high risk of bleeding. The main limitation for the use of LMWHs in PVT is that they require repeated subcutaneous injections for a relatively long period, making such a treatment poorly acceptable by patients and thus likely to cause a high rate of non-adherence. In addition, their efficacy may be jeopardized by the need for antithrombin to ensure the optimal activity of LMWHs, with antithrombin often reduced in the plasma of patients with advanced liver disease. VKAs are still poorly used for the long-term management of PVT because of the perceived risk of bleeding and uncertainty in dosage. These limitations notwithstanding, the recent European Association for the Study of Liver (EASL) guidelines advise LMWHs at therapeutic doses for the initial treatment of acute PVT, followed by VKAs for six months, provided adequate prophylaxis for gastrointestinal bleeding is implemented [9]. A recent study investigating a small group of patients with acute PVT treated sequentially with LMWH plus VKAs showed that the target INR (2.0–3.0) can be reached with VKAs doses similar to those used for non-cirrhotic subjects [10].

The direct oral anticoagulants (DOACs) that inhibit thrombin (dabigatran) or activated factor X (rivaroxaban, apixaban, edoxaban) appear in principle appealing alternatives to VKAs and LMWHs in patients with PVT, because they can be given orally and do not usually require laboratory monitoring to adjust drug dosage. However, they are currently prescribed off-label, because patients with liver disease were deliberately excluded from the randomized clinical trials that led to the licensed use of DOACs in patients with venous thromboembolism or atrial fibrillation.

After an early report of the successful use of these drugs in very few cases of cirrhosis [11], a larger series of these patients was evaluated retrospectively by Intagliata et al. [12]. In their clinical records they identified and described 20 patients with cirrhosis treated for various clinical reasons with apixaban ($n = 11$) or rivaroxaban ($n = 9$). DOACs were administered at full therapeutic daily dosages (10 mg apixaban or 20 mg rivaroxaban) in 15 patients, the remaining 5 patients being prescribed lower dosages (5 mg apixaban or 10 mg rivaroxaban daily).

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The average age of patients was 57 years, they had only A and B Child-Turcotte-Pugh (CTP) scores (the more severe cirrhosis patients with CTP score C were excluded), and the average duration of anticoagulation was 267 days. Two thirds of the patients were treated with DOACs after they had developed PVT, but non-splanchnic thrombosis or atrial fibrillation were additional indications for the prescription of anticoagulants. The rate of documented bleeding events was not trivial, because major bleeding occurred in 5% of the DOAC-treated patients (4 of 20): one case of non-fatal intracerebral hemorrhage, 2 gastrointestinal and one vaginal bleeding. Even though there was no evidence of drug-induced liver injury, the relatively high rate of bleeding complications observed indicates that larger cohorts of cirrhosis patients should be investigated in order to truly evaluate the risk of bleeding and other adverse events associated with DOACs.

In the frame of the aforementioned paucity of data on the effectiveness and safety of DOACs in cirrhosis patients, and particularly in those prescribed anticoagulants after they developed PVT, this issue of the journal reports the results by Hanafy et al. [13] in the frame of a clinical trial comparing the DOAC rivaroxaban with the VKA warfarin in 80 patients with compensated cirrhosis (CTP scores A or B) due to hepatitis C viral infection, who had developed acute PVT. The advantages of this study are not only the relatively large sample size, but also the random allocation of the 80 enrolled patients to low-dose rivaroxaban (10 mg daily) or to warfarin monitored by means of the INR. The most striking finding is that, in spite of the relatively low daily dosage of rivaroxaban (10 mg), objective recanalization of the portal vein was obtained in as many as 85% of cases, in contrast with the 45% recanalization rate in patients treated with warfarin, the latter being similar to that previously reported with anticoagulants. In addition, short-term survival in treated patients was nearly double (20.4 months) in DOAC-treated than in warfarin-treated patients (10.6 months). Importantly, the authors report that the rate of bleeding complications, and particularly of gastrointestinal bleeding, was much higher in patients treated with warfarin (43%), whereas those treated with rivaroxaban experienced no episode of bleeding.

All in all, these results obtained in Egypt (a country with a high prevalence of advanced liver disease, due to viral hepatitis as well as to schistosomiasis) are promising. The high rate of early recanalization despite the use of a relatively low dosage of rivaroxaban is probably due to the fact that per protocol patients were treated very soon after the diagnosis of acute PVT (within one week). This approach is obviously due to a particularly favorable setting of the two Egyptian liver units that accrued the patients in the study, and indirectly emphasize the problems associated with an often delayed diagnosis due to the elusive non-specific symptoms of PVT, that is often asymptomatic in the acute phase [4]. Of course, these data need confirmation in larger studies, but the suggestion that DOACs may be used efficaciously and safely at dosages lower than those used to treat venous thrombosis of the lower limbs is encouraging. Indeed, there is still a high degree of reluctance to use full dosage anticoagulation in patients at high risk of bleeding, such as those with cirrhosis, also noticed in a recent survey carried out in the frame of the centers belonging to the consortium of the Vascular Liver Disease Interest Group (VALDIG) [14].

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