Anticoagulation to prevent disease progression in patients with cirrhosis

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Conflict of interest

SP serves on the speaker bureau for AbbVie and Gilead and has served on their advisory board. AM serves on the speaker bureau for AbbVie and has served on the advisory board for AbbVie and Gilead.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

SP led the study concept and design. SP, AM, and HD equally contributed to acquisition of data, analysis, and interpretation of data. SP led initial drafting of the manuscript, and AM and HD edited the manuscript. All authors reviewed the manuscript for important intellectual content, gave final approval of data, and are accountable for the work.

Supplementary data

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To the Editor:

We read the individual patient data meta-analysis on anticoagulation for cirrhotic non-tumoral portal vein thrombosis (PVT) in relation to survival by Guerrero and coworkers with interest.[1] This study may be a game-changer in the clinical management of PVT, as it suggests that anticoagulation substantially improves survival *independently* of portal vein recanalisation with an acceptable bleeding risk. Interestingly, and in line with other meta-analyses,[2] the effect of anticoagulation on portal vein recanalisation is not very impressive, with 58% of patients recanalising with anticoagulation, while 33% of patients recanalise without anticoagulation. The modest effect of anticoagulation on recanalisation may be explained by recent observations showing that portal vein thrombi frequently do not universally consist of a true thrombus, but rather are related to thickening of the portal vein wall intima.[3] Portal vein intimal fibrosis may not be susceptible to anticoagulant therapy, which targets the coagulation system.

Despite a relatively modest effect of anticoagulation on portal vein recanalisation, all-cause mortality was strikingly reduced in patients on anticoagulation (25% *vs*. 39%, a relative risk reduction of 36%). Importantly, the effect of anticoagulation was independent of PVT severity or recanalisation, but was proportional to duration of anticoagulant treatment. As previous studies have demonstrated that PVT *per se* does not affect progression of disease,[4] these data strongly suggest that anticoagulation has a PVT-independent effect on outcome. Thus, this study suggests that portal vein recanalization should not be considered as a primary goal of anticoagulant treatment in patients with cirrhosis and PVT.

The authors mention that the survival benefit of anticoagulation may be related to prevention of macro- and microvascular thrombosis. The beneficial effect of anticoagulation in the absence of PVT recanalization emphasizes the likely role of the hemostatic system in pathogenesis and progression of liver diseases. Indeed, evidence from experimental settings suggests multiple mechanisms coupling components of the hemostatic system, including coagulation proteases, to the progression of chronic liver disease. Protease activated receptor (PAR)-1 and -2 have been shown to drive hepatic fibrosis, with most studies focusing on direct activation of hepatic stellate cells to a myofibroblast phenotype. In addition, both PAR-1 and PAR-2 have been shown to amplify hepatic steatosis and inflammation in a variety of models. The impact of PAR signaling on intrahepatic blood flow, perhaps related to construction of sinusoidal blood flow by stellate cells, may be of equal importance. The activation of coagulation may exaggerate the formation or persistence of microthrombi in the sinusoids across the liver lobule, negatively affecting tissue perfusion, exacerbating injury, and impeding access to leukocytes essential for repair. These concepts have been reviewed elsewhere.[5] Pathologic roles of VWF and platelets have been noted in multiple experimental settings, and fibrin may also contribute, although its role is less well defined.[6,7] The findings of Guerrero and coworkers emphasize the need to further define these mechanistic connections and pathologic consequences of increased coagulation within the liver microvasculature. Indeed, the dominant therapeutic action of heparin in this patient population may extend well beyond correction of PV occlusion.

The authors conclude that 'PVT may identify a group of patients with cirrhosis that benefit from long-term anticoagulation'. This conclusion is perhaps too narrow. Both preclinical studies and clinical observations suggest a survival benefit of anticoagulant therapy in patients with cirrhosis without PVT.[8,9] We thus feel that it is not the PVT *per se* that will identify patients who may benefit from long-term anticoagulation. We encourage studies to identify those subgroups of patients with advanced disease in whom outcome of disease is likely to be impacted by anticoagulant therapy. We propose that in those patients in whom a potential survival benefit justifies an increased bleeding risk, long-term anticoagulation requires consideration, preferably in the context of well-designed clinical trials.

Unfortunately, studies aimed at testing the effect of anticoagulation on progression of chronic liver disease have proven difficult: one randomized-controlled trial assessing low molecular weight heparin in France (Childbenox) was prematurely discontinued because of a low rate of enrollment, and one randomized-controlled trial in Spain (clinicaltrials.gov NCT02643212) has recently been completed without reaching the planned number of inclusions. Hopefully, the encouraging results of the current study by Guerrero and coworkers will set the stage for additional randomized studies, preferably with direct oral anticoagulants, which have a good safety profile in patients with Child-Pugh A and B cirrhosis and are more suitable for long-term use than low molecular weight heparin. Of note, the concept of clinical anticoagulation to improve survival in patients with cirrhosis was already suggested over a decade ago. In a provocative paper, it was argued that a combination of drugs, specifically an anticoagulant, a beta blocker, a statin, and an antibiotic, may delay decompensation and improve survival.[10] Whereas such a polypill approach may still be a bridge too far, we feel the time has come to extensively trial anticoagulant drugs for this purpose.

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Authors' contributions

TL and JPL drafted the letter, TL WB and JPL revised the initial draft and approved the final version.

Supplementary data

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