



Anti-thrombin III in treatment of Portal vein thrombosis in cirrhotics: have we found the ideal agent?

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Contrary to the general belief, cirrhosis is no longer considered a hypocoagulable state. Instead, decreased levels of coagulation inhibitory factors tilt the balance towards hypercoagulability in cirrhosis (1).

Development of portal vein thrombosis (PVT) is not uncommon in the natural history of cirrhosis. The risk of developing PVT in the patients with cirrhosis is more than seven-fold above the risk in the general population (2). Cumulative incidence of PVT in cirrhotics as shown in a large longitudinal study of 1,243 patients was 4.6%, 8.2% and 10.7% at 1, 3 and 5 years, respectively. This study also showed that development of PVT is associated with the severity of liver disease at baseline and does not follow a recent progression of liver disease (3). Clinical presentation of PVT ranges in from being incidentally detected to presenting with serious complications. It is often difficult to establish a temporal relationship between specific symptoms and development of PVT. Incidence of PVT in a study by Amitrano *et al.* was 11.2% of patients developed PVT and in this study, 57% patients presented with symptoms which included GI bleeding or abdominal pain (4).

The clinical presentation of PVT varies depending on whether it is acute or chronic thrombosis. In patients with acute PVT involvement of the mesenteric veins and its branches may lead to intestinal ischemia or infarction. Clinical presentation of patients with chronic PVT often present with features of portal hypertension, which may include gastroesophageal varices, GI bleeding, splenomegaly and hypersplenism.

The clinical impact of PVT on the natural history of the cirrhosis has been the subject of debate and many studies have tried to evaluate it. It is believed that PVT in liver cirrhosis could lead to decompensation and increased mortality. Luca *et al.* in their study found that progression of thrombosis did not lead to increase in mortality in cirrhotic patients with non-malignant PVT (5). In another study by Nery *et al.*, the authors concluded that there was no evidence that the development of PVT was responsible for further progression of liver disease (3). A recent study also confirmed that PVT does not seem to worsen the prognosis of cirrhosis (6).

The effect of PVT on patients' survival after liver transplantation (LT) is still controversial (7). Two recent large studies one from United Network for Organ Sharing registry and other study using data from the Scientific Registry of Transplant Recipients and Organ Procurement and Transplantation Network have showed that LT waiting list patients with PVT have lower mortality than those without PVT and presence of PVT does not increase mortality in waiting-list patients (7,8).

As the controversy persists surrounding the impact of PVT on natural history and mortality in patient with cirrhosis; the need, timing and duration of treatment is not well defined. Baveno VI guidelines states that anticoagulation should be considered in potential LT candidates with thrombosis of the main portal vein trunk or progressive PVT. In non-candidates for LT anticoagulation could be considered in cases with extension to superior

mesenteric vein and/or known “strong” prothrombotic conditions. Overall the level of evidence and grade of recommendations for management of PVT in cirrhosis as given by Baveno VI guidelines are very weak (9).

Low molecular weight heparin (LMWH), vitamin K antagonists (VKAs) and direct acting oral anticoagulants (DOACs) are currently available options for medical line of treatment for PVT in cirrhotics. Efficacy and safety of LMWH and VKA has been demonstrated in studies (10-12). Overall, the data on treatment of PVT in cirrhotics with LMWH or VKAs is not of high quality and is controversial. Long-term effects of LMWH and VKAs in cirrhotic patients have not been systematically evaluated in studies.

Also VKA and LMWH have some pitfalls. Firstly, VKA leads to overestimation of the Model for End Stage Liver Disease score, which is important for organ allocation. Another issue is regular monitoring of international normalized ratio (INR) for patients on VKA. For LMWH, subcutaneous administration might be a limitation, especially for long term use. Moreover, the accumulation of LMWH in renal dysfunction, a frequent problem in decompensated cirrhosis, may occur and lead to over anticoagulation (12). DOACs appear to be an attractive alternative to VKAs and LMWHs due to their oral route of administration and the fact that no regular laboratory monitoring is required. The potential advantage of these new drugs is that their mechanism of action is independent of anti-thrombin. However, the available data on the use of DOACs in cirrhotics is still limited (13).

Other treatment modalities for PVT in cirrhotic includes endovascular approach (TIPS with local thrombus aspiration and thrombolysis) and surgical treatment which are invasive and have high complications rates. The available data on these procedures is very limited and lack RCTs. Therapy algorithms for treatment of PVT in cirrhotics in current guidelines are based more on expert opinions rather than on results from RCTs (9).

So there is an urgent need for an agent which is effective, easy to administer, doesn't need monitoring and without risk of bleeding. Previous studies have shown Anti-thrombin III (AT-III) to be effective in prevention may be treatment of PVT in cirrhotic patients (14,15).

The paper by Hidaka *et al.* is the first study of its kind (double blind randomized controlled trial) for determining the efficacy AT-III concentrates in treatment of PVT in patients with cirrhosis. It is a very well planned study with precisely defined inclusion criteria, exclusion criteria and

study end points. This study shows that the proportion of patients with complete response or partial response of the PVT was significantly higher in the AT-III group (55.6%; 20/36 patients) than that in the placebo group (19.4%; 7/36 patients) without significant differences in the adverse events and adverse drug reactions between the two groups. One of the significant advantages of the use of AT-III concentrates is it doesn't increase the risk of bleeding, because AT-III itself is a physiological anticoagulation factor (16).

There are few drawbacks of use of AT-III concentrates. As mentioned by authors of the study, first drawback being the medical cost of AT-III concentrates (1,500 U/day, 5 days: ~\$32,250 in the USA) may be higher than that of LMWH (4,000 U/day, 48 weeks: ~\$2,744 in the USA). Second drawback is the lower recanalization rate using AT-III concentrates than anticoagulants. Based on a recent systematic reviews and meta-analysis, which included eight studies patients with cirrhosis and PVT who receive anticoagulant therapy had recanalization rates of 71% compared to 42% in patients who did not receive anticoagulation ($P < 0.0001$). Patients who received anticoagulants also had reduced progression of thrombosis, without excess of major and minor bleedings and less incidence of variceal bleeding.

Use of AT-III concentrates alone for the treatment of PVT in cirrhotics is still not clear, as anticoagulants are still needed to be given along with AT-III concentrates to maintain the patency of portal vein. Moreover, bleeding risk can no longer be considered a drawback of anticoagulants as the recent meta-analysis suggests that risk of bleeding is not increased with the use of anticoagulants in cirrhotics. Also a recent prospective study has shown that abnormal conventional coagulation tests like INR and platelet count do not predict bleeding risk in cirrhotic patients (17). Regarding the use of VKAs, issue which remains is the monitoring of INR. To avoid it, an interesting solution could be the use of direct thrombin inhibitors.

Controversies regarding the impact of PVT on the natural history of cirrhotics, whether PVT affects the survival of patients with cirrhosis and benefits of anticoagulation in these patients still prevail. AT-III is seems to be agent but whether we can avoid using anticoagulants and whether AT-III will impact the survival needs to elucidated. So, further studies using combination of AT-III and anticoagulants are warranted. Overall, this is an excellent study but the role of AT-III in treatment of PVT in cirrhotics needs further validation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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