



The direct oral anticoagulants in patients with and without liver disease

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Anticoagulants are frequently prescribed agents for the prevention and treatment of many cardiovascular conditions. A large number of clinical studies have shown that these agents can prevent or treat acute or chronic thromboembolic diseases. However, the most important complication of treatment with anticoagulant agents is hemorrhage, which may be serious, may cause long-term debilitating disease, or may even be life threatening (1).

Direct oral anticoagulants (DOACs) directly inhibiting factor Xa (rivaroxaban, apixaban, or edoxaban) or factor IIa (dabigatran) are now approved for a variety of indications in medical patients and are often now preferred to traditional anticoagulants, such as vitamin K antagonists (VKA) or low molecular weight heparin (LMWH) (2).

On the other hand, liver disease (LD) patients are a unique group. This clinical condition is characterized by a complicated picture of altered coagulation, thrombocytopenia, decreased pro- and anticoagulation factors produced by the liver, increased von Willebrand factor, increased pro-coagulant factors (VIII), and at risk for clinically evident hyperfibrinolysis. As a result of hemostatic disequilibrium, the coagulation tendency may contribute to the development of portal vein thrombosis (PVT) in patients with LD (3). The estimated prevalence, frequency and distribution of PVT vary widely between studies. In a large cohort of Sweden autopsies by Ogren *et al.*, a population prevalence of 1% was found (4). The reported

prevalence of nontumorous PVT in patients with cirrhosis is highly variable at 0.6–26%, likely secondary to variable patient selection and diagnostic modality. The incidence of PVT in cirrhosis is less clearly defined, but reported as 16% by Amitrano *et al.* (5) in a group of patients with LD followed prospectively.

The De Gottardi's study is published in this issue with interesting results (6). The aim of this study was to identify indications and reasons for starting or switching to DOACs and to understand incidence of adverse effects, complications and short-term outcome. The investigators studied two groups of patients with and without LD. The main indication for anticoagulation was splanchnic vein thrombosis (75%). Rivaroxaban was used most frequently (83% of the patients). The median duration of follow-up was 15 months in cirrhotic and 26.5 months in non-cirrhotic patients. Adverse events occurred in 17% of patients and included 1 case of recurrent PVT and 5 cases of bleeding. Treatment with DOACs was stopped in 3 cases. Although the sample size in this study is relatively small, these results are promising and suggest that DOACs are relatively safe. Interestingly, Hum *et al.* (7) conducted a retrospective study where they evaluated the efficacy and safety of DOACS compared with traditional anticoagulants. They observed that bleeding events were similar in both groups of patients (10 and 8), but the severity of the bleeding events were more serious in the traditional group than the DOACs

group. It is important to note that rivaroxaban was used in 64% and apixaban in 47% of these patients.

A recent study in cirrhotic patients with Childs-Pugh A or B disease (n=39) (8) the investigators compared the risk of bleeding between patients treated with traditional anticoagulation versus DOACs. The groups were comparable clinically and the investigators found a similar number of cases with bleeding events between the groups. DOACs used in that study were apixaban (55%) and rivaroxaban (45%).

What can we learn from the De Gottardi's study (6)? At the present time, DOACs seem to be another option in cirrhotic patients with PVT. However, more clinical trials are necessary in cirrhotic patients with different liver function and to identify the risk factors leading to adverse effects and serious complications, such as bleeding. In addition, it is also important to understand which DOACs are more or less effective and safe in this population.

Accordingly, we suggest that it is important to consider prophylactic therapy to prevent thrombotic disease in patients with LD who are at high risk of bleeding. This suggestion is supported by the study of Villa *et al.* (9) who showed that low dose, once daily enoxaparin may play a protective role in cirrhotic patients. They estimated the incidence of PVT in patients who received the anticoagulant compared to a control group. The results are impressive; in the period of the study, fewer patients with treatment (enoxaparin) developed PVT as expected but also fewer treated patients developed signs of decompensation and fewer died of liver disease.

Finally, more refined guidelines to use in clinical practice for the management of cirrhosis patients in this context are necessary. The new therapies show desirable advantages such as oral administration, few drug interactions and no need for monitoring. On the other hand, the main disadvantages of DOACs include the lack of large, prospective studies focusing on this group and the absence of reversal agents for all except dabigatran in the event of a life-threatening hemorrhage or call in for transplantation. Interestingly in a very recent study by Intagliata *et al.* (10), reported the first case of the successful use of idarucizumab to reverse the anticoagulant effects of dabigatran during liver transplantation. Clearly, we need further clinical trials to know the relative risk-benefit of DOACs in the setting of chronic liver disease but this approach seems very promising.

In conclusion, De Gottardi's study, provides more data and basis for the design of randomized clinical trials

that allow comparing the safety and efficacy of DOACs compared to low molecular weight heparin or VKA that may bring some reasonable benefit to patients with cirrhosis. We anticipate results of current prospective trials with DOACs in this population and encourage future collaborative and expanded studies in this important and vulnerable patient population (11).

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