Blood Reviews 29 (2015) 127–136

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Is there a rationale for treatment of chronic liver disease with antithrombotic therapy?

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ARTICLE INFO

Keywords:
Chronic liver disease
Cirrhosis
Hemostasis
Thrombosis
Anticoagulation

ABSTRACT

Recent advances in the understanding of the coagulopathy in chronic liver disease have provided a strong support for anticoagulation as a new therapeutic paradigm for patients with cirrhosis. Laboratory studies indicate that the net effect of changes in hemostasis in many patients with chronic liver disease is a hypercoagulable status. In turn, clinical thrombosis is increasingly recognized as a complication of liver disease. When occurring within the liver, thrombosis may even progress the disease course. Exciting preliminary data regarding the potential of low-molecular-weight heparin to slow down the progression of liver disease indicate that this class of drugs may improve outcome without a major increase in bleeding risk. However, this new era for antithrombotic therapy in chronic liver disease is still hindered by a persistent false notion that patients with cirrhosis are "auto-anticoagulated" by their underlying liver disease. In addition, there is insufficient clinical evidence on safety and efficacy of anticoagulant therapy in cirrhosis and the studies conducted so far are limited by small sample sizes, uncontrolled treatment arms, or by their retrospective nature. Finally, a lack of knowledge on how or when to monitor antithrombotic treatment to optimize the risk–benefit ratio has restricted a widespread application of anticoagulant treatment in clinical management algorithms. Nonetheless, by systematically covering possibilities and pitfalls, this review highlights the potential of antithrombotic therapy to improve the quality of life and the clinical outcome of patients with chronic liver disease.

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1. Introduction

Anticoagulant or antiplatelet therapy in patients with chronic liver disease is controversial. For decades, chronic liver disease has been thought to be associated with an increased bleeding risk [1]. Hence, generally, physicians have taught and adopted a cautious approach to invasive procedures for fear of bleeding complications. In contrast, an unrestrictive approach to blood product usage became the rule when surgery was the only option, or when excessive bleeding occurred [2]. It also became (and still is) common practice to evaluate or correct the commonly found abnormalities in routine tests of hemostasis in liver disease as in treating other hemostatic disorders. The underlying rationale is that in order to reduce the bleeding risk or stop the major bleeding, clinical decision making should be based on the same grounds as in other (acquired) coagulopathies [3]. However, over the last decade, concepts of the clinical consequences of the hemostatic changes associated with cirrhosis have changed. Experts now acknowledge that bleeding in many (surgical) cases is more likely due to hemodynamic changes in patients with chronic liver disease than to an underlying hemostatic disorder. They also agree that routine hemostatic tests are poor indicators of a bleeding tendency. Hence, these tests are no longer considered to be an acceptable way to evaluate the hemostatic status of these patients, nor is correction of hemostasis based on routine test results indicated [4,5].

Several new insights may have led to this change in paradigm. First, when compared to coagulopathies characterized by a deficiency in a single coagulation factor, as is the case in the hemophilias, hemostatic alterations in liver disease involve the whole spectrum of coagulation factors. Reduced protein synthesis by hepatocytes in the diseased liver leads to deficiencies in procoagulant factors, but reduced protein synthesis also affects anticoagulant components. Hence at baseline there is a rebalanced system, which is not detected by conventional tests of coagulation [4]. Secondly, the hemostatic phenotype in patients with chronic liver disease is determined by a combination of hemostatic and pathophysiological alterations. Complex interactions, such as endothelial activation, renal failure or active infection among others, may all easily shift the precarious hemostatic equation towards a bleeding or a thrombotic tendency depending on circumstances specific to the individual patient [6]. Routine tests of hemostasis are not designed to or lack the sensitivity to detect these interactions. Finally and probably the most important new insight comes from the observation

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http://dx.doi.org/10.1016/j.blre.2014.10.002
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that patients with chronic liver disease are not "auto-anticoagulated". This means that these patients are not protected from thrombotic events when routine tests of coagulation including the prothrombin time (PT) or International Normalized Ratio (INR) and activated partial thromboplastin time (APTT) are prolonged, or when platelet numbers are low [5,7,8].

In fact, it is increasingly recognized that thrombosis can be a major complicating factor in chronic liver disease and may even contribute to its progression [7,9]. The purpose of this review therefore is to create awareness for thrombosis as an important contributor to morbidity and mortality in patients with chronic liver disease. The first section of this article covers some of the *in vitro* studies, which provided the fundamental new concept of a "hypercoagulable state" in chronic liver disease against the antiquated, but prevailing dogma of "auto-anticoagulation". These experiments also provide elementary knowledge on the pathophysiological mechanisms underlying the increased risk of venous, arterial, and portal vein thrombosis observed in epidemiological and clinical studies of chronic liver disease. These will be addressed in subsequent paragraphs of this study. Additionally, this review discusses the use of anticoagulant agents to treat thrombotic complications and their potential to reduce disease progression in patients with chronic liver disease. However, we would like to stress that the limited clinical data on their efficacy and safety do not always allow to refer to clinical guidelines or to formulate them. Discussions on the possibilities and pitfalls of antithrombotic therapy in patients with chronic liver disease will therefore be in the context of a limited knowledge base.

2. Hypercoagulability in chronic liver disease

The occurrence of thrombosis is determined by a shift in any one of the components of Virchow's triad: blood stasis, endothelial injury, and hypercoagulability. The latter is determined by an imbalance in the physiological equilibrium that regulates coagulation and anticoagulation dynamics. In chronic liver disease, however, it has long been thought that such an imbalance inclines the fragile coagulation equilibrium towards a hypocoagulable state. A possible reason for this is that conventional tests of hemostasis are routinely used to estimate the hemostatic status in patients with chronic liver disease. The INR, for example, was originally designed to measure the anticoagulant effect of warfarin and has some serious drawbacks when it comes to reflecting the physiological sequence of events after activation of the coagulation cascade [10]. It senses variations in the procoagulant factors (F) I, II, V, VII and X, most of which are reduced in liver disease (hence the prolonged INR), but it is insensitive to endogenous anticoagulant factors such as protein C (PC) and antithrombin. These are concomitantly decreased in the plasma of patients with chronic liver disease [4]. In addition, the test is insensitive to hemostatic modulators expressed on the endothelial cell surface, such as thrombomodulin (i.e., the essential endogenous cofactor for thrombin activation of PC). Finally, since it is based on the conversion of fibrinogen to fibrin that starts after as little as 5% of the total amount of thrombin is generated, 95% of generated thrombin is not assessed. This "excess" of thrombin is biologically relevant since it participates in various processes besides propagation of the procoagulant cascade. These include remodeling of the fibrin clot structure, clot lysis inhibition and platelet activation as well as inflammatory and wound healing responses [11].

In vitro testing which completely reflects the physiological environment of blood and blood vessels will probably never be possible. Nevertheless, the above example illustrates that conventional tests are completely unphysiological. They should therefore not be used to assess the complex hemostatic status in patients with liver disease. Newer, "state-of-the-art" tests of hemostasis, often referred to as "close-to-physiological" testing, are now readily available in the research laboratory and have been used to explore the hemostatic function of patients with liver disease under laboratory circumstances. Thrombin generation testing (TGT) is an attractive example in this context. The thrombin generating potential in plasma is determined by the concentration of all the known and unknown clotting factors and inhibitors together with some plasma proteins that modulate the response [12]. As the interaction between the pathophysiology of liver disease and the complex coagulation cascade is largely unknown and clotting factor levels normally vary between individuals, TGT in theory better reflects the global effect of liver disease on hemostasis as compared to the analysis of individual coagulation factor levels. By using plasma of patients with chronic liver disease and by adding soluble thrombomodulin to the test-mixture, Tripodi et al. reported a normal thrombin generation despite a prolonged PT and APTT [13]. The addition of thrombomodulin helped approach a "close-to-physiological" condition as the anticoagulant contribution of endothelial cells could now be incorporated and investigated. Interestingly, in a further study Gatt et al. demonstrated an increased thrombin generating potential in plasma of patients with chronic liver disease, which was associated with resistance to the anticoagulant action of thrombomodulin [14].

The different outcome of studies published by Tripodi and Gatt (i.e., normal versus high thrombin generating potential in plasma) may be attributed to differences in methodology, but probably also to disease severity as evidenced by higher MELD-scores in the cohort included in Gatt's study. Indeed, in TGT, the degree of resistance to thrombomodulin appears to increase with the severity of liver impairment [15,16]. This may be explained by alterations in a number of hemostatic components. For example, PC levels progressively decrease with increasing stages of disease severity, which may lead to a hypercoagulable status in patients with advanced disease. This effect of decreased PC levels on the hemostatic status of cirrhotic patients was recently supported by a study demonstrating that addition of exogenous PC to the thrombin generation assay reverses the resistance to thrombomodulin [17].

Alterations in levels of the procoagulant FVIII may also destabilize the precarious coagulation balance in chronic liver disease. However, in contrast to PC or most other (procoagulant) proteins of the coagulation system, FVIII levels are commonly increased in patients with chronic liver failure [18]. This is partly due to the fact that FVIII is not synthesized by hepatocytes, but by the endothelium [19–22], and upon endothelial stress its plasma levels may increase substantially. Once activated, FVIII is a target protein for activated PC and hence FVIII levels correlate well with thrombomodulin resistance in TGT studies of chronic liver disease [15,16]. Together with alterations in levels of PC and other components of the coagulation system such as antithrombin, changed FVIII levels therefore offer a complementary explanation for the relative hypercoagulability in plasma samples of cirrhotic patients. *In vivo*, however, thrombin generation is not only a function of pro- and anticoagulant factors, but also of platelets [23]. The platelet surface provides a scaffold for the assembly of coagulation factor complexes, and this assembly is an essential step in the thrombin generation pathway. Primary and secondary hemostasis, therefore, are integrated physiologically to facilitate thrombin generation and fibrin formation.

In view of the physiological importance of platelets in supporting coagulation, our group has studied the function of the primary hemostatic system in chronic liver disease. We found that, in a close-to-physiological model using flowing blood, platelet adhesion and aggregation were increased when incubated in plasma of cirrhotic patients, even when the platelet count was adjusted to thrombocytopenic levels [24]. We attributed this to the presence of high levels of the platelet-binding protein von Willebrand factor (VWF). These high VWF levels apparently compensate for the decrease in platelet number and function. Subsequent studies demonstrated a normal-to-increased thrombin generating potential in platelet-rich plasma [23]. When combined, the *in vitro* studies conducted so far with modern tests of hemostatic function therefore substantiate the presence of a general hypercoagulability in chronic liver disease as a consequence of both a

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