We read with interest the recent letter to the editor entitled “Primary Biliary Cirrhosis: Time to Replace a Misnomer” published by Wahl et al. We congratulate the authors for their study based on interviewing new patients and opening again the debate for the name of primary biliary cirrhosis (PBC). The authors concluded that it is time to replace this misnomer with an adequate name for the disease. We agree with the authors’ conclusion. PBC is now diagnosed at an early stage and the majority of patients will never develop cirrhosis. Although we agree with this, the acronym “PBC” is now used since it was first so called in 1965 by Rubin et al. Recently a Monothematic Conference on Primary Biliary Cirrhosis was held in Milan and a beautiful presentation was made by two patient associations. The debate confirmed the results presented by Wahl et al. However, a message has clearly been expressed: “Call it how you want, but please leave the acronym PBC.”

We would like to draw attention to the importance of the PBC acronym for the scientific community, physician, and patients. Yes, it is time to modify the term “cirrhosis” in PBC.

We thank Dr. Levi Sandri for his comment and plea not to change the acronym for primary biliary cirrhosis, “PBC.” PBC has been used for decades as the acronym for primary biliary cirrhosis and has not only been incorporated into textbook knowledge but also into the hearts and names of societies and patient support groups.

We are fully aware of the dilemma and difficulties which a change of the disease name may cause. Both to completely rename as well as to keep the acronym but to remove the term “cirrhosis” seems to have strong pros and cons.

Although it may be difficult to completely replace the name of an established disease, the renaming of vasculitides syndromes according to their etiopathogenesis, size of vessel affected, and type of inflammation demonstrated that this is in principle feasible. From the pathogenetic perspective a term such as autoimmune cholangitis (AC) may be more appropriate without the implication of pending cirrhosis and terminal liver disease. Another reason for defining a new term and a new acronym is that using the established acronym for a new disease term may cause confusion, for example, when looking up the acronym in textbooks or the Internet.

On the other hand, keeping an established and catchy acronym such as “PBC” not only complements the other autoimmune cholestatic liver disease “PSC” but also keeps the link to existing names, institutions, and to the scientific literature. We agree with the authors that it is fundamental to hear the patients’ thoughts on renaming the disease primary biliary cirrhosis since patients are the victims of inadequate naming. If the result of the ongoing discussion within the respective patient organizations was to keep the acronym this would be a strong argument. However, patient interest groups may not always reflect the views of all affected patients, and, thus, their view is one of many to be considered.

If the discussion within patient groups as well as specialists results in the decision to keep the established acronym, we would like to propose as the new name of this disease “primary small bile duct cholangitis.” This name would not only allow keeping the acronym “PBC” but it would at the same time remove the term “cirrhosis” and differentiate the disease from primary sclerosing cholangitis “PSC,” which affects the larger intra- and extrahepatic bile ducts.

Primary Biliary Cirrhosis: Time to Replace a Misnomer

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References


Reply:

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Potential conflict of interest: Nothing to report.

Reference


Decreased In Vitro Anticoagulant Potency of Rivaroxaban and Apixaban in Plasma From Patients With Cirrhosis

To the Editor:

There is increasing interest in treatment and prevention of cirrhotic portal vein thrombosis (PVT) with anticoagulant drugs. Two recent reports in Hepatology suggested efficacy and safety of new-generation oral anticoagulant drugs (the direct factor Xa inhibitors, Rivaroxaban and Apixaban) in treatment of PVT in patients with compensated cirrhosis. These new drugs have
practical advantages over traditional anticoagulants. We recently showed altered in vitro potency of different anticoagulant drugs in patients with cirrhosis, compared to patients with intact liver function. A theoretical risk for excessive anticoagulation when using these drugs in patients with cirrhosis and concomitant alterations in their hemostatic system exists.

We previously demonstrated a decreased in vitro anticoagulant effect of Rivaroxaban in patients with cirrhosis. Using thrombomodulin-modified thrombin generation testing, we examined the in vitro anticoagulant potency of Apixaban, which we compared to the anticoagulant potency of Rivaroxaban. This study protocol was approved by the medical ethical committee of the University Medical Center Groningen (Groningen, The Netherlands), and written informed consent was obtained from each subject before inclusion in the study. We added vehicle, 25 ng/mL of Apixaban, or 50 ng/mL of Rivaroxaban to plasma samples of 11 healthy individuals and 14 patients with cirrhosis (9 patients with Child B cirrhosis and 5 with Child C cirrhosis). We performed thrombin generation tests in the presence of thrombomodulin and calculated the percent decrease in total thrombin generation by the two anticoagulant drugs, as described previously. Whereas a fixed dose of the drugs decreased total thrombin generation in healthy volunteers by 55 ± 6% (Rivaroxaban, mean ± standard deviation) and 51 ± 4% (Apixaban), the mean decrease in thrombin generation in patients was significantly lower (30 ± 9% for Rivaroxaban, P < 0.0001 [t test]; 32 ± 10% for Apixaban, P < 0.0001).

In conclusion, the in vitro anticoagulant potency of Apixaban is substantially reduced in patients with moderate and advanced cirrhosis, similar to the reduced potency of Rivaroxaban, which we previously reported. These results suggest that anticoagulant treatment with these direct factor Xa inhibitors will likely not result in overanticoagulation, with a potentially increased bleeding risk, provided drug levels remain in the target range. Careful monitoring of drug levels, for example, by anti-Xa testing, may be required.

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Reply:
We thank Intagliata et al. and Potze et al. for sharing their clinical experience and in vitro data about the two factor Xa inhibitors, rivaroxaban (Xarelto, Bayer/Johnson & Johnson) and apixaban (Eliquis, Bristol-Myers Squibb/Pfizer). Our report and subsequent response by the authors is reflective of the growing interest in the use of nontraditional anticoagulants for treatment of portal and superior mesenteric vein thrombosis (PVT/SMV) in patients with cirrhosis. Both factor Xa inhibitors exhibit reliable pharmacokinetics and pharmacodynamics, with a linear relation between plasma concentration of the drug and anticoagulant activity. Their plasma half-life is short and is very similar to heparins. Impaired renal function results in a prolonged half-life and increased anticoagulant effect of rivaroxaban much more than apixaban, but otherwise these drugs have similar characteristics with regard to absorption and metabolism.

The report from Intagliata et al. of five patients with compensated cirrhosis (Child-Pugh Class A) emphasizing the safety and efficacy of rivaroxaban and apixaban for treatment of acute PVT/SMV is very encouraging. Similar to our experience (Child-Pugh Class A), complete resolution of the thrombus required a treatment duration of 6 months. No bleeding-related adverse event were observed despite 6 months of therapy. However, data with regard to their use in decompensated cirrhosis is lacking, as manufacturers of both factor Xa inhibitors currently do not recommend the use of these agents in Child-Pugh Class B and C for safety concerns. Interestingly, Potze et al. report a significantly lower in vitro anticoagulant potency of apixaban and rivaroxaban using a thrombin generation assay in plasma from patients with decompensated cirrhosis (Child-Pugh Class B and C). The authors speculate that direct Xa inhibitors will therefore not likely to cause over-anticoagulation in patients with decompensated cirrhosis, and as such may not be associated with increased risk of bleeding and could in fact be associated with treatment failure.

Certain aspects of factor Xa inhibitors deserve further discussion before extrapolation of in vitro data to clinical care. The bioavailability of rivaroxaban is higher than apixaban (80% versus 66%) and is dependent on food intake, as it is strongly lipophilic. Both rivaroxaban and apixaban are highly protein bound (87-95%) and it is quite possible that hypoalbuminemia associated with decreased synthetic function in decompensated cirrhosis may result in more active drug and perhaps more anticoagulant activity. Moreover, decompensated cirrhosis may be associated with decreased creatinine clearance from underlying hepatorenal syndrome. Use of rivaroxaban and not apixaban would be associated with increased anticoagulant activity. While in vitro studies use platelet-poor plasma with the addition of phospholipids as a substitute in the presence of thrombomodulin, these assays only partially mimic in vivo physiology. Studies using whole blood clotting assays such as thromboelastography that reflect overall hemostatic balance would need to be performed to better understand the anticoagulant potency of factor Xa inhibitors in patients with cirrhosis with decompensated liver disease. Alternatively, reliably measuring factor Xa levels may be necessary in cirrhosis patients to ensure therapeutic doses of anticoagulation in order to avoid treatment failure.

Hemostasis is a fine balance between pro- and anticoagulants and despite a lowering of actual levels, the thrombin