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COMMENTARY

An anticoagulant that does not cause bleeding – an abrupt stop on the road to the Holy Grail

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Cardiovascular diseases are major contributors to morbidity and mortality and pose a huge burden to the health care system. Thrombosis is the most common etiology for ischemic heart disease, ischemic stroke, and venous thromboembolism.[1] Over the last 100 years, there has been tremendous progress in the treatment of thromboembolic diseases. Currently, several highly effective anticoagulant options are available for treatment of venous thromboembolism: heparin(s), vitamin K antagonists, or direct-acting oral anticoagulants; however, all anticoagulants pose an increased risk of bleeding. A retrospective market scan study of data collected between 2008 and 2011 in the United States showed that 28% of venous thromboembolism-affected patients experienced bleeding within 1 year after diagnosis, with half of the episodes being a major bleeding event.[2] Even though direct-acting oral anticoagulants are safer with regard to major, fatal, and intracranial bleeding than vitamin K antagonists,[3] the annual rates of major bleeding in clinical practice are still as high as 3% to 4%, as found in a prospective German study of patients who were treated with rivaroxaban.[4]

Hence, although they are extremely effective, the safety of the currently used anticoagulant drugs needs to be improved. The ideal anticoagulant should only target the pathological and unwanted fibrin formation in thrombosis and leave the (thrombin and) fibrin formation in hemostasis unaffected. Over the last years, considerable efforts have been made to find a safe anticoagulant by targeting factors upstream of the coagulation cascade such as factor XI or factor XII.[5] The first human studies targeting factor XI are very promising,[6-8] and in the near-future the potential of this approach will become clear.

A completely different approach for potential safe anticoagulation was identified by chance in a patient who presented with a traumatic subdural hemorrhage and greatly prolonged global plasma coagulation test results (prothrombin time, activated partial thromboplastin time, and thrombin time) due to an anti-thrombin immunoglobulin A paraprotein.[9] Testing of the antibody revealed a specific and high-affinity interaction with the fibrinogen recognition site (exosite I) of thrombin. Although the patient presented with a traumatic bleed, the presence of the paraprotein did not lead to previous or subsequent bleeding episodes. With its specificity to exosite I, the antibody does not interfere with other important interactions of thrombin via its active site or exosite II. The antibody was made recombinantly and changed to a human immunoglobulin G4 (now called JNJ-9375) with identical characteristics compared to the paraprotein.[10] JNJ-9375 inhibited thrombin-induced platelet aggregation but not the aggregation induced by other agonists. There was a small increase in lag time in thrombin generation analyses, but hardly any effects on peak thrombin or the endogenous thrombin potential. This may have been expected from the mode of action of the antibody that interferes with the thrombin-fibrinogen interaction, an interaction that is not tested in thrombin generation. In a rat arteriovenous shunt model of thrombosis, pretreatment with JNJ-9375 dose-dependently reduced thrombus formation with a better safety profile than its comparator apixaban.[10] The logical next step was therefore to test the antibody for thrombosis prophylaxis during orthopedic surgery. In this issue of the *Journal of Thrombosis and Haemostasis*, Weitz et al[11] tested the antibody in a double-blind, double-dummy phase 2 trial in patients undergoing knee arthroplasty in the Targeting Exosite-1 Thrombin Inhibition-Total Knee Replacement (TEXT-TKR) study.

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The half-life after intravenous infusion in humans is 3 to 4 weeks, allowing a single dose of JNJ-9375 for prophylactic indications. The patients received a single postoperative infusion of JNJ-9375 in doses ranging from 0.3 to 1.8 mg/kg or twice-daily apixaban. In contrast to expectation, JNJ-9375 was associated with nearly threefold higher venous thrombosis rates compared to apixaban. The rate of thrombosis was independent of the dose of JNJ-9375, although thrombin times were dose-dependently prolonged. On the safety side, the number of bleeding events was similar for the JNJ-9375 and apixaban arms. As with the efficacy endpoint, there was no dose response with JNJ-9375 treatment. Given the negative results of the dose-escalating study, the second part of the trial (a dose-response study) was not started.

With the promising *in vitro*[9,10] and animal data,[10] the failure of JNJ-9375 in the TEXT-TKR study comes as a surprise. Although it is not known what the explanation for this observation is, several reasons may be possible. With its specificity to exosite I, JNJ-9375 may be less potent than other thrombin-targeting agents.[11] However, this same property was one of the attractive characteristics as it would make JNJ-9375 a safer anticoagulant. Second, in the clinical trial, JNJ-9375 was given after surgery, which is different from the preclinical models, where the antibody was given prior to the initiation of a thrombus. It is possible that the antibody can inhibit thrombus formation, but not prevent growth of an already-existing thrombus. Third, the preclinical models did not precisely match the injury of the patients in the clinical trial. Total knee replacement involves a large wound area with excessive tissue factor exposition to blood.[12] It may be that in situations with high tissue factor, JNJ-9375 is less potent in inhibition of fibrin formation. An indication may have already been that the prothrombin time, a test initiated with a high concentration of tissue factor, was much less prolonged in the patient with the paraprotein than the thrombin time or activated partial thromboplastin time.[9] The rat arteriovenous shunt model that demonstrated efficacy of JNJ-9375 is a model mainly driven by contact activation,[10] and may therefore not be representative of the situation during knee replacement.

What are the consequences of the negative trial findings with the anti-thrombin antibody JNJ-9375? It seems unlikely that the antibody can be used for treatment or prevention in all thrombotic situations, but there still may be interesting options. In the past, starting prophylaxis with low-molecular-weight heparin preoperatively was not associated with a lower incidence of venous thromboembolism than starting postoperatively, and perioperative regimens increased the risk of postoperative major bleeding.[13] However, with JNJ-9375 thought to be very safe, it may still be worthwhile to investigate whether a preoperative or perioperative start of the compound reduces the risk of venous thromboembolism without the cost of major bleeding. Furthermore, JNJ-9375 may be an interesting option to prevent medical device thrombosis where current direct-acting oral anticoagulant therapy failed.[14]

This trial clearly underlines the challenges in drug development in general, and even more so in finding a new anticoagulant that is effective but does not cause bleeding.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

J. C. M. M. and S. M. prepared the manuscript.

LINKED CONTENT

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