TB-402 for the prevention of venous thromboembolism in orthopaedic surgery: Something new and promising, or not?

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Certain patient groups are at high risk of developing venous thromboembolism (VTE), and those undergoing major orthopaedic surgery have a particularly high risk of postoperative deep-vein thrombosis (DVT) and pulmonary embolism (PE) without appropriate antithrombotic prophylaxis (1, 2).

Low-molecular-weight heparin has been extensively used in the prevention of VTE in orthopaedic surgery, since it reduces the rate of thromboembolic events without increasing the risk of major bleeding complications. In the last few years, antithrombotic prophylaxis in this setting experienced a great progress with the development of the novel oral anticoagulant drugs (NOAC) (3). The NOACs are orally administered and have a predictable anticoagulant effect, which allows fixed dose regimens without the need for routine laboratory monitoring or dose adjustment. Dabigatran, rivaroxaban and apixaban have therefore been included in the latest edition of the American College of Chest Physicians (ACCP) guidelines, for VTE prevention after elective total hip replacement (THR) or total knee replacement (TKR) (4). Further improvement in the setting of antithrombotic prophylaxis may be obtained with a drug that produces a stable and prolonged anticoagulant effect after a single administration.

TB-402 is a human monoclonal antibody with promising pharmacological properties. Preclinical data suggest that the partial inhibition of factor VIII (FVIII) activity, obtained with TB-402, may provide the same antithrombotic efficacy of complete FVIII inhibition, while avoiding excessive anticoagulation (5). The maximal inhibition of FVIII reached with TB-402 in vitro is approximately 40-70%, irrespective of the excess of the antibody over FVIII (6). As a result, increasing the dose of the drug will only prolong the duration of the effect, minimising the risk of overdosing. In healthy volunteers, TB-402 administered as a single intravenous bolus, demonstrated a very long half-life of about three weeks, arising the possibility of a prolonged and stable anticoagulant effect (6). Moreover, various procoagulants have been shown to restore the normal coagulation in vitro (7) and may be used as antidotes to reverse the pharmacologic effect of this long-acting anticoagulant drug in clinical practice.

A phase II study investigating the safety and efficacy of TB-402 after TKR has been recently published (8). In this dose-escalating open-label trial with blinded endpoint adjudication, 316 patients were post-operatively randomised to a single intravenous dose of TB-402 (0.3, 0.6 or 1.2 mg/kg, administered 18-24 hours [h] after surgery) or subcutaneous enoxaparin (40 mg, administered 6-8 h after surgery and afterwards once-daily for at least 10 days). In the evening pre-operatively, all patients received subcutaneous enoxaparin. The primary efficacy endpoint, symptomatic VTE and asymptomatic DVT, was evaluated by bilateral venography up to day 7-11. All tested doses of TB-402 were associated with a lower rate of VTE compared with enoxaparin, even though the reduction was statistically significant only for the 0.3 mg/kg dosage. The principal safety outcome, major and clinically relevant non-major bleeding, was observed in 4.0%, 5.4% and 8.0% for the three increasing TB-402 doses and in 3.8% for the enoxaparin group. The two lowest dosages of TB-402 had similar incidence and timing of bleeding compared with enoxaparin, since all the events occurred within the first nine days after surgery; in the 1.2 mg/kg dosage group, instead, bleeding events were numerically higher and occurred until 28 days after surgery, indicating a longer exposure to the anticoagulant effect.

In the current issue of Thrombosis and Haemostasis, Verhamme et al. report the results of a phase II double-blind double-dummy randomised controlled trial investigating the efficacy and safety of TB-402 for VTE prevention after THR (9). A single dose of TB-402, 25 or 50 mg administered as intravenous infusion 2-4 h post-operatively, was compared with rivaroxaban 10 mg, administered orally once-daily for 35 days. Fixed doses of TB-402 used in this study were derived from the two lowest doses used in the TKR study (25 mg and 50 mg correspond to 0.3 mg/kg and 0.6 mg/kg, for subjects with mean body weight of about 80 kg). The antithrombotic strategy using TB-402 was as effective as the comparator rivaroxaban. The primary efficacy outcome, symptomatic VTE and asymptomatic DVT detected by bilateral venography at day 35, was observed in around 5% of subjects in each group. On the other hand, TB-402 was associated with a higher risk of bleeding. Indeed, the principal safety outcome, major and clinically relevant non-major bleeding, occurred in 5.8% and 7.2% for the TB-402 25 mg and 50 mg, respectively, versus 1.4% in the rivaroxaban group. The majority of bleeding events were surgical site related and occurred within 14 days after surgery.
Reasons for the disappointing difference in the safety of TB-402 in these two trials should be discussed. Both studies are phase II randomised controlled trials, at low risk of bias, and could be certainly considered of high quality. The study investigating TB-402 in THR was double-blind double-dummy (9), while the design for TB-402 in TKR was open-label with blinded endpoint adjudication (8). Although it is well known that an open-label design may induce information bias, the outcome assessment, blinded for the allocated treatment, may provide the same accuracy as a double-blind design with less inclusion bias (10, 11). Interestingly, the comparator treatment differed between the two studies. TB-402 was compared with the current standard of care, subcutaneous enoxaparin, in the TKR trial (8), and with the NOAC rivaroxaban in the THR trial (9). For the first time, a NOAC has been chosen as the comparator treatment.

After being evaluated in the RECORD programme, four phase III randomised controlled trials for VTE prevention after THR (12, 13) and TKR (14, 15), rivaroxaban has become a new option for extended prophylaxis in orthopaedic surgery (4). In a pooled analysis of these trials, rivaroxaban 10 mg once-daily was more effective than enoxaparin, administered at different dosages and lengths, in reducing the incidence of symptomatic VTE and all-cause mortality (0.5% and 1.0% for rivaroxaban and enoxaparin, respectively, p=0.001). On the other hand, the use of rivaroxaban was associated with a similar rate of major bleeding and of the composite endpoint constituted by major and non-major clinically relevant bleeding events compared to enoxaparin (0.3% vs 0.2%, p=0.23 and 2.8% vs 2.5%, p=0.19, respectively) (16). In the study evaluating TB-402 in THR (9), the definition of major bleeding was wider, as it included surgical site bleedings associated with a fall in haemoglobin ≥ 2 g/dl or transfusion ≥ 2 blood units but not leading to re-operation, which were not included in the RECORD trials. Notably, these bleeding events occurred only in the two TB-402 groups, whereas no major bleeding occurred in the rivaroxaban group (9).

Furthermore, the dosing regimens of TB-402 used in these two studies presented some peculiar characteristics. In the TKR trial, TB-402 was administered the morning after surgery, at least 18 h and no later than 24 h after wound closure, and all patients received a pre-operative dose of enoxaparin (8). On the contrary, in the THR trial fixed doses of TB-402 were administered 2-4 h after wound closure (9). Although the partial inhibition of FVIII might attenuate the propensity for bleeding, the early post-operative administration of TB-402, performed in order to optimise its antithrombotic effect, resulted in a higher number of bleeding events. The appropriate timing of antithrombotic prophylaxis after orthopaedic surgery has been the object of several debates (17, 18). Since in the surgical setting most of the bleeding events are wound related, early administration of TB-402, not unexpectedly, caused higher bleeding rates.

In conclusion, TB-402 is a promising new parenteral anticoagulant, characterised by a single-dose regimen. Its partial inhibition of FVIII may protect from excessive bleeding tendency, while targeting a common risk factor for VTE (19). In the clinical study, published on this issue of *Thrombosis and Haemostasis*, TB-402 confirmed its efficacy also in patients undergoing THR, since very few thromboembolic events were observed and no PE- or VTE-related death occurred (8, 9). On the other hand, the THR study showed higher bleeding rates with TB-402 compared with rivaroxaban. Although the long-standing anticoagulant effect of TB-402 may be reversed by different concentrations of factor VIII, its safety in clinical practice remains to be established and further studies are warranted to clarify the adequate timing of antithrombotic prophylaxis with this compound after orthopaedic surgery.

**Conflicts of interest**

None declared.

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