Rivaroxaban: direct factor Xa inhibition to treat acute deep vein thrombosis

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Traditionally, unfractionated heparin with overlapping vitamin K antagonist administration formed the mainstay of venous thromboembolism treatment (i.e. deep vein thrombosis or pulmonary embolism).

More recently low molecular weight heparins have provided a more convenient treatment (Breddin et al, 2001). Nevertheless, long-term treatment with a vitamin K antagonist is a major challenge as it requires regular laboratory monitoring since it interacts with other drugs and food (Kearon et al, 2008). Considerable morbidity and mortality is associated in particular with proximal deep vein thrombosis (Baglin et al, 2010), with a long-term risk of recurrent venous thromboembolism following cessation of treatment (Douketis et al, 2010).

A once-daily oral anticoagulant with no or little food and drug interactions which does not require regular blood monitoring would be an ideal acute and long-term treatment option. Rivaroxaban inhibits free, fibrin-bound factor Xa and the prothrombinase complex with dose-dependent predictable pharmacokinetics and pharmacodynamics, unlike heparin (unfractionated and low molecular weight) which indirectly inhibits factor Xa by binding to antithrombin (Borris, 2009).

Rivaroxaban is a novel oral, direct factor Xa inhibitor which was better than enoxaparin for preventing venous thromboembolism in more than 12 500 patients undergoing elective total hip or total knee replacement (RECORD clinical programme: REgulation of Coagulation in ORthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism) (Fassiadis, 2009).

The EINSTEIN programme consists of three controlled randomized phase III trials for the treatment of acute, symptomatic deep vein thrombosis (EINSTEIN-DVT), treatment of pulmonary embolism (EINSTEIN-PE) and long-term secondary prevention of recurrent venous thromboembolism in patients who have been treated for deep vein thrombosis or pulmonary embolism (EINSTEIN-EXTENSION). The first two trials were integrated into a single protocol analysing rivaroxaban's efficacy *vs* enoxaparin and vitamin K antagonists in patients suffering from an acute deep vein thrombosis or pulmonary embolism, following two dose-finding feasibility trials with rivaroxaban for the management of patients with deep vein thrombosis (Agnelli et al, 2007; Buller et al, 2008).

EINSTEIN-DVT included 3449 patients: 1731 were assigned to rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily for the rest of the study) and 1718 patients to subcutaneous enoxaparin followed by vitamin K antagonist for 3, 6 or 12 months. The rivaroxaban group had non-inferior efficacy with respect to primary outcome (recurrent venous thromboembolism) with a comparable principal safety outcome (major bleeding or clinically relevant non-major bleeding) in each group (Bauersachs et al, 2010).

EINSTEIN-EXTENSION included 602 patients who received rivaroxaban and 594 who received placebo, and showed superior efficacy in the rivaroxaban group with an acceptable small risk of non-fatal major bleeding in 0.7% of patients (Bauersachs et al, 2010). Results are eagerly awaited from the ongoing EINSTEIN-PE and two further phase III trials: the ROCKET-AF study which evaluates the efficacy of rivaroxaban compared to warfarin for the prevention of systemic thromboembolism in patients with non-valvular atrial fibrillation and the MAGELLAN study which analyses rivaroxaban *vs* enoxaparin for the prevention of venous thromboembolism in patients admitted to hospital for medical illnesses. BJHM

KEY POINTS

- Venous thromboembolism is a significant cause of death.
- Rivaroxaban, a novel oral anticoagulant, is currently being evaluated for its efficacy in preventing and treating venous thromboembolism.

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