Rivaroxaban—a Novel, Oral Anticoagulant for Thromboprophylaxis after Major Orthopaedic Surgery

A report by

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Rivaroxaban is a novel, oral, direct factor Xa (FXa) inhibitor in advanced clinical development for the prophylaxis and treatment of thromboembolic disorders. By acting at the pivotal point of the coagulation cascade, where inhibition of one molecule of FXa prevents the generation of approximately 1,000 thrombin molecules, rivaroxaban effectively reduces the risk of thrombus formation. Rivaroxaban is a promising alternative to the pharmacological strategies currently available for prophylaxis against venous thromboembolism (VTE)—manifesting as deep vein thrombosis (DVT) or pulmonary embolism (PE). VTE is a well-recognized, serious risk after major orthopedic surgery.

Although the therapies employed routinely for the management of thromboembolic disorders are effective, they have intrinsic properties that make them difficult to use in both the inpatient and outpatient setting. Vitamin K antagonists (VKAs), such as warfarin, have a delayed onset of action and a narrow therapeutic window, as well as an unpredictable pharmacological profile, all of which necessitate frequent coagulation monitoring. The potential for a multitude of drug-drug interactions with warfarin make its use potentially even more problematic. The low molecular weight heparins (LMWHs) require parenteral administration, and thus are inconvenient and costly for outpatient care. Rivaroxaban is anticipated to overcome these limitations by providing oral, predictable, and effective thromboprophylaxis after elective surgical procedures, such as total hip replacement (THR) or total knee replacement (TKR), using fixed dosing, and without the need for monitoring.

This review discusses phase II findings of rivaroxaban for prophylaxis against VTE after major orthopedic surgery. These findings have resulted in the initiation of an extensive phase III program in this indication, and suggest that welcome advances in antithrombotic therapy may be on the horizon.

**Clinical Studies—Prophylaxis against Venous Thromboembolism after Major Orthopaedic Surgery**

In early clinical studies in healthy subjects, rivaroxaban was consistently well tolerated, with a rapid onset of action, as well as predictable pharmacokinetics and pharmacodynamics. It has a half-life of five-nine hours in healthy young subjects, increasing to 12–13 hours in elderly subjects. After multiple rivaroxaban doses, no clinically relevant changes in bleeding time, blood pressure, heart rate, electrocardiogram, or vital signs were observed. In addition, rivaroxaban did not prolong the Q-T corrected (QTc) interval. Rivaroxaban also demonstrated a low propensity for interactions with commonly used medications, including aspirin and non-steroidal anti-inflammatory drugs. Furthermore, it is likely that fixed doses of rivaroxaban may be given to patients irrespective of age, gender, or body weight.

Results of phase I studies confirmed that rivaroxaban was suitable for further investigation, and led to four large, phase II dose-finding clinical trials being conducted in over 4,000 patients undergoing elective THR or TKR. In all of these studies, the primary efficacy end-point was defined as the composite of any DVT, non-fatal, symptomatic PE, and all-cause mortality. The secondary efficacy end-point was the incidence of major VTE, defined as the composite of proximal DVT, PE, and VTE-related death.

The primary safety end-point was the incidence of major post-operative bleeding—defined as bleeding starting more than six hours after surgery, or after the first post-operative dose of study drug (whichever came first), but no later than two days after the last administration of study drug. Major post-operative bleeding included: fatal bleeding; bleeding into a critical organ; bleeding leading to re-operation; bleeding warranting treatment cessation; and clinically overt bleeding (above expected levels) leading to a 2g/dL fall in hemoglobin, or transfusion of >2 units of blood.

**Proof-of-principle Study**

The first of these phase II trials was an open-label, phase IIa proof-of-principle study of rivaroxaban conducted in patients undergoing THR. The efficacy and safety of oral rivaroxaban—2.5–30mg twice daily (BID) and 30mg once daily (OD)—initiated post-operatively were...
compared with subcutaneous LMWH enoxaparin—40mg OD initiated before surgery. Standardized, mandatory, bilateral venography was performed after patients had received study drugs for five-nine days. Rivaroxaban reduced the incidence of the primary efficacy end-point, and there was a dose trend with increasing rivaroxaban doses (p=0.0504). Furthermore, a significant dose-response relationship was observed for major VTE (p=0.0108). As would be expected, the incidence of major post-operative bleeding increased dose dependently with rivaroxaban (p=0.0008). Results with rivaroxaban 30mg OD were consistent with the dose-response relationships between the BID doses and all end-points, suggesting that OD rivaroxaban dosing could be feasible. When efficacy and safety were considered together, rivaroxaban compared favorably with enoxaparin, and demonstrated proof-of-principle for prophylaxis against VTE in patients undergoing elective THR.

Twice-daily Rivaroxaban Dose-finding Studies

Following the favorable results with the rivaroxaban BID doses in the phase IIa study, two separate phase IIb, double-blind, BID dose-finding studies were conducted. These were large, randomized, active-comparator-controlled (versus enoxaparin), parallel-group studies investigating a 12-fold dose range of rivaroxaban (total daily doses 5–60mg) given BID in patients undergoing primary THR (n=722) or TKR (n=621), in Europe and North America, respectively. The incidence of the primary efficacy end-point observed with rivaroxaban was similar to that observed with enoxaparin, across the dose range investigated. The incidence of major VTE was also similar to that observed with enoxaparin (see Table 1), and no deaths were reported in either study. There was a significant dose-response relationship between rivaroxaban and major post-operative bleeding in both studies (p<0.05), with a similar incidence observed in the rivaroxaban 5–20mg dose groups and enoxaparin group. In these short-term trials, rivaroxaban had no adverse effects on electrocardiogram (ECG) parameters, and there was no evidence of compromised liver safety. These studies were designed to allow a pooled analysis of the results, which confirmed that when efficacy and safety were considered together, the total daily dose of rivaroxaban 5–20mg compared favorably with enoxaparin.

Once-daily Rivaroxaban Dose-finding Study

While the two phase IIb BID studies were taking place, further evidence became available suggesting that a more convenient OD regimen of rivaroxaban may be feasible. The results of pre-clinical and clinical pharmacology studies indicated that the pharmacodynamic effects of rivaroxaban persist for up to 24 hours after OD dosing. Furthermore, a clinical
pharmacology study investigating any potential interaction between rivaroxaban and enoxaparin showed that rivaroxaban 10mg had similar pharmacodynamic effects to enoxaparin 40mg, with measurable effects at 24 hours. Although the half-life of enoxaparin is short, at only 4.1 hours, OD dosing has been shown to be highly effective for prophylaxis against VTE after major orthopedic surgery. The results of these studies, in addition to the efficacy and safety of the 30mg OD dose in the proof-of-principle study, led to the initiation of a phase IIb study investigating the efficacy and safety of rivaroxaban 5–40mg given OD for prophylaxis against VTE after THR. This was a large, randomized, double-blind, active-comparator-controlled (versus enoxaparin), parallel-group dose-finding study in patients undergoing elective, primary THR.

OD rivaroxaban demonstrated similar efficacy to enoxaparin (see Table 1). The observed incidence of the primary efficacy end-point across the eight-fold dose range evaluated was lower with rivaroxaban than with enoxaparin (6.4–13.5% versus 25.2%). Although there was a tendency towards a dose-response relationship between rivaroxaban and the primary efficacy end-point, it was not statistically significant (p=0.0825). However, there was a significant dose-response relationship between rivaroxaban and major VTE (p=0.0072). Furthermore, the observed incidence of major VTE was lower with all rivaroxaban doses (0.9–2.7%) than with enoxaparin (2.8%), except for the 5mg dose (the lowest effective dose), in which the incidence of major VTE was 8.5%.

There was a significant dose-response relationship between rivaroxaban and major post-operative bleeding (p=0.039). However, there were no significant differences between any rivaroxaban dose and enoxaparin (although the study was not powered to show the differences between individual doses). The two lowest doses of rivaroxaban, 5 and 10mg OD, had similar rates of major post-operative bleeding to enoxaparin (2.3% and 0.7% versus 1.9%, respectively). Importantly, all major post-operative bleeding events were confined to the surgical site, and there were no cases of fatal bleeding or bleeding into a critical organ. No treatment arm was stopped due to safety concerns or lack of efficacy. When safety and efficacy were considered together, rivaroxaban 10mg OD was defined as the optimal dose—a dose within the range identified in the BID studies.

Safety and Tolerability

Rivaroxaban was well tolerated in these phase IIb studies, with a safety profile similar to enoxaparin. Fixed doses of rivaroxaban were given to all patients, irrespective of age, gender, or body weight. After short-term use in the post-surgical setting there was no evidence of compromised liver safety. Furthermore, the incidence of elevated liver transaminases with rivaroxaban was generally lower than that observed in the enoxaparin groups. Rivaroxaban had no effect on ECG or laboratory parameters (except clotting tests). Only a low incidence of nausea and vomiting with early post-operative rivaroxaban administration was reported.

The Future of Rivaroxaban

An extensive phase III program has been initiated following the success of phase II clinical trials in demonstrating the efficacy and safety of rivaroxaban for prophylaxis against post-operative VTE. The REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of DVT and PE (RECORD) program was designed to confirm the efficacy and safety of rivaroxaban 10mg OD in this indication. The four studies will investigate short and long-term prophylaxis in approximately 10,000 patients in North America and the European Union, and will be used to support the filing for rivaroxaban for prophylaxis against VTE after major orthopedic surgery.

Rivaroxaban is also being investigated in long-term and chronic indications, with phase III studies initiated for VTE treatment and the prevention of stroke in patients with atrial fibrillation, and phase II studies initiated for the secondary prevention of acute coronary syndromes.

Conclusion

Anticoagulation is the standard of care for prophylaxis against VTE after major orthopaedic surgery. Although current antithrombotic agents are effective, they are inherently inconvenient and unpredictable—constraints which may be overcome by rivaroxaban, a novel, oral, direct FXa inhibitor. Phase II studies investigating rivaroxaban for thromboprophylaxis after major orthopedic surgery demonstrated that it had efficacy and safety similar to subcutaneously administered enoxaparin. In addition, rivaroxaban can be given once daily as a fixed dose, irrespective of age, gender or body weight, making it convenient for use across numerous indications, in both inpatient and outpatient settings. With rivaroxaban now at an advanced stage of clinical development, surgeons may be able to look forward to the prospect of a once-daily, oral anticoagulant that does not require monitoring, potentially allowing reliable, effective care from hospital to home.

A version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchmusculoskeletaldisease.com).