PostScRxipt - ExtRa

NHS Greater Glasgow and Clyde

No. 15 AUGUST 2009

RIVAROXABAN – A NEW ORAL ANTICOAGULANT

- **Two new oral anticoagulant agents, rivaroxaban and dabigatran, are licensed for the prevention of venous thromboembolism (VTE) in adults undergoing elective hip or knee replacement surgery.**
- **Rivaroxaban has been added to the *Greater Glasgow & Clyde Formulary*. Currently, dabigatran is not on the *Formulary.***
- **At present there is not an NHSGGC protocol which outlines the exact place in therapy for rivaroxaban.**
- **Rivaroxaban is administered orally at a fixed dose and does not require any monitoring.**
- **Initial studies have shown rivaroxaban (10mg per day), to be superior to SC enoxaparin (40mg per day) for the prevention of VTE in patients following elective hip or knee replacement surgery.**
- **Initial studies did not show any statistically significant difference in bleeding risk with rivaroxaban compared to enoxaparin, however, further studies are required to confirm this.**
- **There are no studies comparing rivaroxaban with aspirin.**
- **If prescribed within NHSGGC, the full treatment course of rivaroxaban should be supplied from hospital prior to discharge.**

Introduction

Rivaroxaban is a new oral anticoagulant and is a factor Xa inhibitor. Factor Xa inhibition, inhibits thrombin production and the formation of clots. Rivaroxaban is licensed for the prevention of venous thromboembolism (VTE) in adults (>18yrs) undergoing elective hip or knee replacement surgery. The recommended treatment dose is 10mg per day for a duration of five weeks in patients undergoing a hip replacement and 10mg per day for two weeks in patients following a knee replacement. The first dose should be taken 6 to 10 hours post surgery, providing haemostasis has been established. It has a rapid onset of action with maximum concentrations being achieved within 2 to 4 hours following administration. No anticoagulation monitoring is required.[1]

Dabigatran, the other new oral anticoagulant, is a direct thrombin inhibitor. It is also licensed for the prevention of VTE in adults undergoing elective hip or knee replacement surgery. Unlike rivaroxaban, dabigatran has not shown superiority to enoxaparin in initial studies. However, in two large phase III studies dabigatran was reported to be non-inferior to enoxaparin.[2] There are no direct comparative data between dabigatran and rivaroxaban. Dabigatran is at present non-formulary within NHSGGC.[3]

Evidence

Three randomised, placebo-controlled, double-blind phase III studies compared rivaroxaban 10mg orally once a day with subcutaneous enoxaparin 40mg per day (RECORD 1,2,3).[4-6] The RECORD (Regulation of Coagulation in Orthopaedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism) study programme involved over 12,500 patients.[4-7] RECORD 1 and 2 included patients undergoing elective total hip replacement (THR) surgery[4,5] and RECORD 3 included patients undergoing elective total knee replacement (TKR) surgery.[6] There was a fourth RECORD study (RECORD 4) which was based in the US.[7] However, the dose of enoxaparin used is different from the UK licensed dose for the prevention of VTE and therefore the RECORD 4 study is not considered within this bulletin.

The primary efficacy outcome in all three studies was the composite of any deep vein thrombosis (DVT), (symptomatic or asymptomatic), non fatal pulmonary embolism (PE) and all-cause mortality. The main secondary efficacy outcome was major VTE (composite of proximal DVT, non-fatal PE or death from VTE).[4-6]

The primary safety outcome was the incidence of major bleeding beginning after the first dose and up to 2 days after the last dose of the study drug (on-treatment period). Major bleeding was defined as bleeding that was fatal, occurred in a critical organ or required re-operation or extrasurgical-site bleeding associated with a fall in haemoglobin or that required transfusion.[4-6]

All three studies were designed to test for non-inferiority which if demonstrated in the per-protocol population, resulted in a test for superiority being performed in the modified intention-to-treat (mITT) population (patients who had undergone surgery, taken a study drug, and undergone adequate assessment for VTE).[8]

Total Hip Replacement

In RECORD 1, both rivaroxaban and enoxaparin were given for 35 days following THR surgery (range 31 to 39 days). In the mITT population (n=3153), the primary efficacy outcome occurred in 1.1% of the rivaroxaban group and 3.7% of the enoxaparin group, absolute risk reduction (ARR) 2.6%, 95% CI 1.5-3.7, p<0.001, relative risk reduction (RRR) 70%, 95% CI 49-82, p<0.001. In the mITT population (n=3364), the secondary endpoint occurred in 0.2% of the rivaroxaban group compared to 2% of the enoxaparin group, ARR 1.7%, 95% CI 1-2.5, p<0.001, RRR 88%, 95% CI 66-96, p<0.001. For the safety analysis (n=4433), major bleeding occurred in 0.3% of the

rivaroxaban group and 0.1% of the enoxaparin group (p=0.18). There was one episode of fatal bleeding in a patient randomised to the rivaroxaban group, however,

this occurred during surgery prior to the administration of rivaroxaban.[4]

In RECORD 2, rivaroxaban was given for 31-39 days (mean duration 33.5 days) and enoxaparin was given for 10-14 days (mean duration 12.4 days) following THR surgery. The aim of the study was to determine whether 5 weeks extended duration thromboprophylaxis with rivaroxaban was superior to 2 weeks prophylaxis with enoxaparin. In the mITT population (n=1733), the primary efficacy outcome occurred in 2% of the rivaroxaban group and 9.3% of the enoxaparin group, ARR 7.3%, 95% CI 5.2-9.4, p<0.0001. In the mITT population (n=1923), the secondary endpoint occurred in 0.6% of the rivaroxaban group compared to 5.1% of the enoxaparin group, ARR 4.5%, 95% CI 3-6, p<0.0001. For the safety analysis (n=2457), major bleeding only occurred in one patient in each group (p=0.98) and the incidence of any on-treatment bleeding was 6.6% in the rivaroxaban group compared to 5.5% in the enoxaparin group (p=0.25). There were no episodes of fatal bleeding with either drug. [5]

Total Knee Replacement

In RECORD 3, both rivaroxaban and enoxaparin were given for 10-14 days following TKR surgery. In the mITT population (n=1702), the primary efficacy outcome occurred in 9.6% of the rivaroxaban group and 18.9% of the enoxaparin group, ARR 9.2%, 95% CI 5.9-12.4, p<0.001, RRR 49%, 95% CI 35-61, p<0.001. In the mITT population (n=1833), the secondary endpoint occurred in 1% of the rivaroxaban group compared to 2.6% of the enoxaparin group, ARR 1.6%, 95% CI 0.4-2.8, p=0.01, RRR 62%, 95% CI 18-82, p=0.02. For the safety analysis (n=2459), major bleeding occurred in 0.6% of the rivaroxaban group compared to 0.5% of the enoxaparin group (p=0.77). There were no episodes of fatal bleeding with either drug. [6]

A pooled analysis of the four RECORD studies was presented as a conference abstract at the 50th Meeting of the American Society of Hematology in December 2008. This analysis corroborated the data obtained in the individual studies regarding reduction of total VTE, major VTE and symptomatic VTE.[9]

Ongoing Studies

There are other studies ongoing to assess rivaroxaban for different indications including acute coronary syndrome, the treatment of VTE, and VTE prophylaxis in medical patients. Rivaroxaban is also being compared to warfarin for the prevention of stroke in patients with non valvular atrial fibrillation.[10]

Safety

Although initial studies have shown the incidence of bleeding with rivaroxaban to be comparable to enoxaparin, further study is required to assess the risk. Low rates of bleeding were reported in the RECORD studies, however, this may be due to the definition of bleeding used. Surgical site bleeding wasn't included unless it led to re-operation or death. The studies also excluded patients with a high risk of bleeding.

In RECORD 2 there was an excess of cardiovascular events on discontinuing rivaroxaban.[5] This was not shown in the other studies, however, the possibility of rebound activation of coagulation warrants further research.

The most common adverse events reported with rivaroxaban include an increase in the liver enzymes, gamma-glutamyltransferase and transaminases, anaemia, nausea and post-procedural haemorrhage (including post-operative anaemia, and wound haemorrhage). Refer to the Summary of Product Characteristics for full details of cautions and contraindications.[1]

Place in Therapy

Rivaroxaban is on the *Formulary* restricted to specialist use. However, the place in therapy of rivaroxaban within NHSGGC has not been decided. A protocol for VTE thromboprophylaxis in orthopaedic surgery is awaited.

If rivaroxaban is prescribed, the full recommended treatment course should be supplied from hospital prior to discharge. The discharge prescription should be clear in communication to GPs and community pharmacists that the full supply has been given and no further supply is required.

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