Clinical Medicine Insights: Blood Disorders

REVIEW

Update on Rivaroxaban

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Abstract: Anticoagulants are recommended for the prevention and treatment of venous thromboembolism (VTE). The new anticoagulants which target specific factors in the coagulation cascade offer the advantage that they can be administered orally. These drugs seek to offer safe anticoagulation without the need for regular monitoring and frequent dose adjustment. Some of these newer drugs are in the advanced stages of clinical trials or have already completed them and thereby aim to provide more options in the management of thromboembolism. In the present review we discuss the currently available evidence supporting the use of these new anticoagulants, in particular rivaroxaban.

Keywords: rivaroxaban, antithrombotic agents, venous thromboembolism, factor Xa, thrombin

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Introduction

Arterial and venous thromboembolism continue to be a major cause of death and disability in the developed world with increasing incidence now noted in the developing world.[1] Heparin and warfarin have formed the basis for the prevention and treatment of thromboembolism for more than fifty years.[2]

Warfarin is a Vitamin K antagonist (VKA), preventing post-translational modification of several coagulation proteins. Unfractionated heparin primarily stimulates the activity of anti-thrombin III thereby inhibiting the function of factors Xa and thrombin. Low Molecular Weight Heparin (LMWH) has fewer side effects[3] but still needs to be given parenterally. Millions of patients take anticoagulants on a daily basis for atrial fibrillation, stroke prevention, treatment or prevention of DVT and pulmonary embolism or as part of the necessary regimen for those with mechanical cardiac valves. In spite of the proven efficacy of these agents,[4] they have several drawbacks and do not fulfill the definition of the ideal anticoagulant.[5]

The parenteral route of administration for unfractionated heparin and LMWH makes these agents inconvenient and costly to use outside the hospital setting. This is because a regular visit by a healthcare professional is necessary if the patients are unable to self administer due to illness, frailty or reluctance.[6] Warfarin has a well documented efficacy for the prevention of venous thromboembolism (VTE) after orthopaedic surgery and stroke prevention in patients with atrial fibrillation[7] but is limited by the narrow therapeutic window, with significant risks of haemorrhage at therapeutic concentrations.[8] Other significant factors resulting in limitation in clinical practice, include numerous drug and food interactions, slow onset of action, and the need for frequent laboratory monitoring to minimize the risk of inadequate anticoagulation or haemorrhagic events.[9]

These limitations of warfarin have fostered a great interest in the development of novel anticoagulants for oral use to potentially replace warfarin. The design of specific inhibitors against molecular targets that play a pivotal role in the coagulation cascade has been the basis for a rational strategy for oral anticoagulant development.[10] The principal molecular targets are factor IIa (thrombin) and factor Xa. A number of detailed review articles on the development of these oral anticoagulants has been recently published, shedding light on this fast growing field.[11,12]

Mechanism of action, metabolism and pharmacokinetic profile

The three overlapping phases of coagulation include initiation, priming and propagation.[13,14] Factor VII gets activated on a tissue factor bearing cell and the activated complex then activates factor IX, X and V to generate a small amount of thrombin (IIa). Factor IIa generated from the initiation phase then activates the platelets and the factors V, VIII and XI, and an activated complex is formed on the platelet surface in the priming phase. In the propagation phase the activated factors on the platelet surface from the priming phase generate a large amount of thrombin to form a clot with fibrin.[13]

Rivaroxaban (Bayer HealthCare AG and Johnson & Johnson Pharmaceutical Research and Development, L.L.C.) is a once-daily, oral, novel oral anticoagulant, which works by directly inhibiting the active site of Factor Xa of the human coagulation cascade. It selectively and competitively binds to FXa thereby blocking the interaction of FXa with its substrate prothrombin. Binding inhibits not only free FXa but also fibrin-bound FXa and prothrombinase activity.[15,16]

After oral administration, it is absorbed in the stomach and small intestine with a bioavailability of 60% to 80%. Peak plasma levels are achieved in 3 hours, and the drug circulates with a half-life of 9 hours. Rivaroxaban is cleared via 2 pathways: 66% is eliminated through the biliary/faecal route and 33% is excreted unchanged through the renal route.[17] Maximum plasma levels of rivaroxaban occur 2–4 hours after oral administration and elimination of rivaroxaban from plasma occurs with a terminal half-life of 5–9 hours in young individuals, and 11–12 hours in the elderly.[18]

Clinical Studies

Rivaroxaban for prophylaxis

Rivaroxaban represents a credible alternative to the present LMWH regimens for prevention of VTE after hip or knee arthroplasty, the two surgical situations associated with the highest postoperative thromboembolic risk. This FXa inhibitor has been evaluated in four phase III large-scale studies for thromboprophylaxis following major orthopaedic surgery, **RE**gulation of

Coagulation in major **O**rthopaedic surgery reducing the **R**isk of **D**VT and PE **(RECORD)** program, in a dose of 10 mg once a day commenced postoperatively. The outcome was measured as primary efficacy outcome (the composite of DVT, PE and all-cause mortality) with relative risk reduction and the primary safety outcome (major bleeding).

The **RECORD 1 trial** compared the efficacy and safety of rivaroxaban with enoxaparin in patients undergoing hip arthroplasty.[19] Patients received either oral Rivaroxaban,10 mg once a day (od), started 6–8 hours after surgery, or subcutaneous enoxaparin 40 mg od, started on the evening before surgery. Both rivaroxaban and enoxaparin was continued for a duration of five weeks. The primary efficacy outcome was recorded in 18/1595 (1.1%) of patients treated with rivaroxaban compared with 58/1558 (3.7%) of those receiving enoxaparin ($P < 0.001$), demonstrating a relative risk reduction (RRR) of 70%. The primary safety outcome was similar in both groups (6/2209 [0.3%] with rivaroxaban vs. 2/2224 [0.1%] with enoxaparin).[19]

In **RECORD 2**, a five week prophylactic regime of rivaroxaban was compared with 10–14 days of prophylaxis with enoxaparin (followed by placebo for a total of five weeks), for prevention of VTE after THR in 2509 patients.[20] Oral rivaroxaban 10 mg od was commenced 6–8 hours after surgery and the enoxaparin group received subcutaneous injection 40 mg once a day starting from the evening before surgery. The primary efficacy outcome occurred in 17/864 (2.0%) of patients in the rivaroxaban group compared with 81/869 (9.3%) in the enoxaparin group ($P < 0.0001$) group, demonstrating an RRR of 79%. Major bleeding was encountered very infrequently and was similar in those receiving extended prophylaxis with rivaroxaban and short-term enoxaparin (1/1228 [0.1%] vs. 1/1229 [0.1%], respectively.[20]

The **RECORD 3** trial evaluated oral rivaroxaban (10 mg od) with subcutaneous enoxaparin (40 mg od) for the prevention of VTE after TKR in 2531 patients.[21] Both groups received the drugs for 10–14 days. The primary efficacy outcome (total VTE) was significantly reduced in the rivaroxaban group. Secondary efficacy end points (major and symptomatic VTEs) occurred less frequently with rivaroxaban but the differences did not reach statistical significance. Rivaroxaban patients showed similar rates of major bleeding as compared to enoxaparin patients (0.6% to 0.5% respectively).[21]

RECORD 4 compared once-daily oral rivaroxaban (10 mg) with twice-daily subcutaneous enoxaparin (30 mg) for VTE prophylaxis after TKR in 3148 randomized patients.[22] Both the drugs were administered for period of 10–14 days. The primary efficacy outcome was the same as for **RECORD3** and occurred in significantly fewer patients in the rivaroxaban group. The rate of major bleeding was 0.7% in the rivaroxaban group as compared to 0.3% in the enoxaparin group (insignificant difference $P = 0.11$).

Thus all the **RECORD** trials have shown that rivaroxaban is more effective than enoxaparin for the prevention of VTE in patients undergoing major orthopaedic surgery. Complications of bleeding and hepato-toxicity were extremely low.

Rivaroxaban for treatment of DVT

Rivaroxaban has now been assessed for VTE treatment in the dose finding phase II **EINSTEIN-DVT** and **ODIXa-DVT** (**O**ral **DI**rect factor **Xa** inhibitor in patients with acute symptomatic **D**eep **V**ein **T**hrombosis) trials.[23,24]

The **ODIXa-DVT** trial randomised patients with acute DVT to twice daily doses of 10, 20 or 30 mg or once daily dose of 40 mg of rivaroxaban or to the standard treatment of enoxaparin and vitamin-K antagonists for 12 weeks. The primary efficacy outcome of reduction in thrombus burden on day 21, recurrent VTE or VTE related death did not differ significantly differ between the rivaroxaban and standard treatment groups.[23]

The **EINSTEIN-DVT** trial randomised patients with DVT to receive 20, 30 or 40 mg of rivaroxaban once daily or standard treatment with enoxaparin followed by vitamin K antagonists for three months. The primary outcome of the study were symptomatic venous thrombo-embolic complications and asymptomatic deterioration of thrombus burden as measured by quantitative ultrasound. No significant difference was noted in the primary outcome in any of the four groups nor in the bleeding episodes between the groups.[24]

The phase III of the **EINSTEIN** study was designed to evaluate the efficacy of rivaroxaban in the treatment of acute symptomatic DVT (**EINSTEIN-DVT)** or PE **(EINSTEIN-PE)**. The extension

arm **(EINSTEIN-Extension)** of the trial was to investigate the role in preventing recurrent VTE after 6–12 months of treatment.

Rivaroxaban is being further evaluated in other ongoing phase III studies which include VTE prophylaxis in medically ill patients (MAGELLAN; **M**ulticenter r**A**ndomised parallel **G**roup **E**fficacy and safety study for the prevention of VTE in hospitalised medically i**LL** patients comparing rivaroxab**AN** with enoxaparin), and comparison with warfarin for stroke prevention in patients with AF (**ROCKET AF**; **R**ivaroxaban **O**nce daily oral direct factor Xa inhibition **C**ompared with vitamin **K** antagonist for the prevention of stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation).[25]

In phase II **ATLAS ACS TIMI (** **A**nti Xa **T**herapy to **L**ower cardiovascular events in addition to **A**spirin with/without thienopyridine therapy in subjects with **A**cute **C**oronary **S**yndrome in collaboration with the **T**hrombolysis **I**n **M**yocardial **I**nfarction group) **46** Trial, 3491 recent acute coronary syndrome patients were initially treated with aspirin alone (no-761) or with aspirin plus clopidogrel (no-2730). The patients were further randomised to placebo or rivaroxaban therapy in a number of dosing regimens for 6 months. Death, MI and stroke was significantly less in the rivaroxaban group of patients than in the placebo group. Major bleeding was encountered in significantly more rivaroxaban patients, while there was no gross evidence of drug-induced liver injury with rivaroxaban.[26]

Safety

Rivaroxaban has been shown predictable pharmacokinetics and pharmacodynamics across patients of different ethnic origin.[27,28]

In healthy subjects, gender and body weight does not alter the pharmacokinetics and pharmacodynamics of rivaroxaban suggesting that the prophylactic dose of 10 mg OD does not require dose adjustment for extremes of weight.[29]

The inter-individual variability of rivaroxaban in pharmacokinetic parameters has been noted to be minimal after meals[30] The pharmacokinetic profile of the drug has not shown any difference with simultaneous use of pH lowering agents, rantidine or antacids.[30]

The metabolic route of rivaroxaban can predict potential drug—drug interactions but individual reactions vary. Two-thirds of the drug is metabolised by CYP3A4, CYP2J2 and CYP450-independent mechanisms before elimination.[31] It is also as substrate for P-glycoprotein transporters. No clinically relevant interaction was noted with digoxin (a p-Glycoprotein substrate) or ranitidine (a weak CYP450 inhibitor).[30,32] The concomitant use of CYP3A4 inhibitors like ketoconazole is contraindicated.[31] The simultaneous use of non-steroidal anti-inflammatory drugs (NSAID) or aspirin will expectedly be common in clinical practice and has an increased bleeding risk which however, has not been found to be clinically significant.[33] The product recommendation is to use NSAIDs with caution.[31]

More information regarding the effect of adding rivaroxaban to asprin with or without clopidogrel will be available at the conclusion of the phase III of the ATLAS ACS TIMI trial.

There is a direct dose–response relationship between rivaroxaban and major postoperative bleeding ($P = 0.0008$).[34] However although concomitant use of enoxaparin and rivaroxaban in prophylactic doses show an additive anti-factor Xa activity there is no increased risk of bleeding.[35]

Efficacy

Although several studies have shown safety and efficacy of single daily dose of rivaroxaban in the management of VTE,[36,37] the US FDA has declined to approve the once daily rivaroxaban regimen for the prevention of deep venous thrombosis and pulmonary embolism in patients undergoing hip and knee replacement due to concerns about the risk of bleeding and possible hepatotoxicity. However, the drug, at a dose of 10 mg once daily, has been recommended for thrombo-prophylaxis for the same in the NICE guidelines published in January, 2010 (www.nice.org.uk).

Patient perspective

Patient non-compliance to anticoagulation therapy is common in clinical practice.[38] Patients receiving warfarin require frequent monitoring and dose adjustments to achieve the desired therapeutic range (target INR usually 2–3) and many patients even

in trials have the INR out of the target range.[39,40] Inability to achieve target INR could have serious consequences as the risks of bleeding and other haemorrhagic events are increased if the INR is above the target range where as under-anticoagulation leads to augmented risks of recurrent VTE and stroke.[41–43]

The numerous food and drug interactions with VKAs may lead to adverse events[44] and patients may have to endure dietary restriction or discontinuation of other medications for effective anticoagulation. Frequent dose adjustments or complex dosing regimens can be confusing, particularly for elderly patients, where non-compliance can be a particular problem.[45,46]

Although UFH, LMWHs, and fondaparinux are easier to manage than VKAs, they require parenteral administration, which is inconvenient for use in the community. UFH has also the extra disadvantage of requiring regular coagulation monitoring and is also associated with HIT and osteoporosis. Hence, the requirement for monitoring during VKA and UFH therapy dictates regular visits to clinics and potential disruption to daily routine.[47]

Conclusion

In summary, prophylaxis with rivaroxaban not only demonstrated non-inferiority, but was significantly more effective than prophylaxis and with enoxaparin after THR and TKR as shown in the RECORD trials. These trials have shown that there is a slightly increased incidence of bleeding and hepatotoxicity in patients on rivaroxaban.

There is the lack of dietary interactions and a predictable dose response. Drug interaction is very minimal and there is no need of monitoring of bleeding parameters. The phase III of the EINSTEIN trials will give us more information on treatment of DVT with rivaroxaban.

Authors' Contributions

Osama Moussa was involved in the writing the paper and providing evidence and references. D. Chattopadhyay has been involved in checking and revising the draft. Vish Bhattacharya is the responsible consultant surgeon who had set the management plan and revised and rewritten the paper.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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