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An Overview of Rivaroxaban and its role invenous thromboembolism

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Abstract: *Venousthromboembolism is a disease which is a combination of deep vein thrombosis and pulmonary embolism. Multiple treatment and prophylactic modalities are available, ranging from pharmacological to mechanical options. One of the pharmacological options available involved in the treatment and prophylaxis of venous thromboembolism are oral anti coagulants which is used in the treatment and prevention of venous thromboembolism and one of them is rivaroxaban. Rivaroxaban is an oral selective direct factor Xa inhibitor having high oral bioavailability andswift onset of action. It has a fixed dose regimen and has been revealed to be as effective as standard anticoagulant therapy involved in the treatment and prevention of venous thromboembolism without the need of regular laboratory monitoring.*

A better understanding of the uses of the above mentioned drug is gained which helps in supporting the theory that their use can be helpful in supplementing the treatment and prophylaxis of venous thromboembolism. Rivaroxaban clearly have a role to play in the treatment and prophylaxis of venous thromboembolism. Studies have depicted and provide support to the idea that rivaroxaban are effective in an individual therapy for treatment of venous thromboembolism and also in prophylaxis. Going forward more targeted study is required for rivaroxaban working and benefits for gaining a clearer consensus which would help in better incorporation of this modality in the management of venous thromboembolism.

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I. Introduction

Venous thromboembolism is a disease which comprises of a group of disorders which includes deep vein thrombosis and pulmonary embolism which is a lethal and common disorder that affects both hospitalized and non-hospitalized patients. Pulmonary embolism and Deep vein thrombosis exist as the two clinical expositions of venous thromboembolism and share similar predisposing aspects. In majority of incidences, Deep vein thrombosis leads to pulmonary embolism [1]. Deep vein thrombosis is defined as astate of establishment of a blood clot in the deep veins [2]. Although it mostly occurs in the deep veins of the distal limbs, it may also occur in other sitesin addition to the deep veins of the proximal limbs, the vena cava [2]. Venous thrombosis is described through the Virchow's triad which hypothesized three factors for its formation and propagation including blood stasis in vessel wall, hyper coagulationdisorders and last of all the vessel wall abnormalities [1]. The symptoms of deep vein thrombosis which are erythema, pain and oedema, occur in the acute phase of deep vein thrombosis [3]. Pulmonary embolism occurs due to dislodgement and the migration of a portion of thrombus from the limb to the lungs resulting in the thrombus occluding the pulmonary artery which inturn requires an urgent intervention. Pulmonary embolism is usually the most common cause of hospitalization post-surgery or trauma [4]. The chronic complication of deep vein thrombosis presents with the complains of pain, swelling and ulcers which together is labelled as post thrombotic syndrome(PTS) presenting in almost half of the deep vein thrombosis patients within two years of the onset of deep vein thrombosis [5].

II. Treatment

The treatment methods these days are directed towards relieving these complications like recurrent episodes of deep vein thrombosis, pulmonary embolism, post thrombotic syndrome and eventually death [3]. Among the multiple treatment alternativesavailable for the treatment of deep vein thrombosis ranging from pharmacological and interventional therapies to compression therapies and mechanical thrombolytics, which are administered according to the needs and requirements of the patients [6]. A number of prophylactic options are also available for venous thromboembolism like the mechanical modalities (Graduated compression stockings and Intermittent pneumatic compression devices), pharmacological options like low molecular weight heparin, warfarin, rivaroxaban and these options have been proven to be effective in treatment and prophylaxis of venous thromboembolism when used as a single drug therapy or in combination therapy.

Pharmacological management

The pharmacological therapies involved in management of venous thromboembolism includes administration of anticoagulants orally or through parenteral routes which act by preventing additional clot build up and allows the patient's innate fibrinolytic mechanisms to lyse the pre-existing clot. Low molecular weight heparin, and indirect factor Xa inhibitors like fondaparinux which are chemically related to Low molecular weight heparin, unfractionated heparin, Vitamin-K antagonists like warfarin and coumarins and Directly acting oral anticoagulant which includes direct activated factor Xa inhibitors like Rivaroxaban, apixaban and Direct thrombin inhibitors like dabigatran are some of the anticoagulants prescribed in management of venous thromboembolism.

This article will be focusing on the properties and the role of the drug Rivaroxaban a factor Xa inhibitor in prevention and prophylaxis of Venous thromboembolism.

III. Rivaroxaban

Mechanism of action

Rivaroxaban belongs to the class of oral anticoagulants prescribed during the treatment but mainly in prophylaxis of venous thromboembolism. Rivaroxaban is a direct activated factor Xa inhibitor. The drug exerts its desired anti thromboembolic effect by preventing the formation of thrombin by directly inhibiting factor Xa. Rivaroxaban has found to inhibit factor Xa with 10,000-fold higher selectivity than for other biologically relevant serine proteases. Rivaroxaban inhibits both free and clot bound factor Xa, as well as prothrombinase activity unlike the indirect factor Xa inhibitors such as fondaparinux. Rivaroxaban binds directly at the active site of factor Xa and blocks its contact with its substrate thereby inhibiting thrombin generation which in turn leads to prevention of the conversion of fibrinogen to fibrin. It also does not require cofactors like antithrombin to exert its anticoagulant effect [7] [8].

Pharmacokinetics

It has a predictable pharmacokinetic profile with high oral bioavailability (80-100%) and rapid absorption and prompt onset of action with maximum plasma concentrations achieved in 2-4hours following its administration. The presence of high bioavailability of rivaroxaban displays a lack of presystemic loss of drug that is, cytochrome P450(CYP) 3A4 and P-glycoprotein(P-gp) transporter are not involved in the absorption of rivaroxaban. Maximal plasma concentration (Cmax) in rivaroxaban is achieved rapidly in 2-4 hours following a single dose (1.25-80mg) and multiple doses (up to 30 mg two times a day). Following subsequent multiple dosing, rivaroxaban is not known to accumulate to a relevant extent. In many previously held clinical trials rivaroxaban was found to be highly specific, well tolerated and equally as effective as other drugs used in standard of care [8] [9]. Rivaroxaban is found to have no food interactions and is known to have limited drug interactions compared to the other drugs prescribed in management of venous thromboembolism like low molecular weight heparin and vitamin K antagonists like warfarin [8] [9]. Compared to other oral anticoagulants used in management of venous thromboembolism of rivaroxaban is administered in fixed prescribed doses and does not require frequent laboratory monitoring of coagulation parameters like international normalised ratio(INR), prothrombin time and partial prothrombin time (PPT). Drugs like low molecular weight heparin and warfarin require frequent monitoring of their coagulation parameters like international normalised ratio and prothrombin time[10] [11] [12] [13] [14] [15] [16] [17]. Patients when treated with low molecular weight heparin are found to have elevated International normalised ratio they are shifted to warfarin. Rivaroxaban proves beneficial in this aspect as regular monitoring of coagulation parameters is not required when utilized [12] [13] [14] [15] [17]. It is orally administered hence it isunderstandably much simpler to take and adhere and is allied with better compliance compared to low molecular weight heparin and other pharmacological drugs used in the management of venous thromboembolism which are usually administered through a parenteral route [13] [14] [17].

Metabolism and Excretion

Rivaroxaban is the subject of metabolism by cytochrome P450 enzymes (CYP3A4/5, CYP2J2) and CYP-independent ways [18] [19]. CYP3A4 is involved in about 18% and CYP2J2 in about 14% of total rivaroxaban elimination. Additionally, to this oxidative biotransformation, non-CYP-associated hydrolysis of the amide bonds represents 14% of total elimination of rivaroxaban [18]. The metabolites are removed by the kidneys and by the hepatobiliary system [20].

Excretion of rivaroxaban occurs via two systems in one of which the kidneys act by removing unchanged drug and in other degradation of the agent takes place along with metabolic transformation [19]. Around half of the administered dose is removed in unchangedform as an active substance via urineand the other half via faeces [9] [20].

Indications

Keeping in mind the above mentioned points and factors rivaroxaban is preferred to be used in young people or people of <65yrs of age and healthier venous thromboembolism patients having a better renal profile which would aid in elimination of the drug from the body and low rates of adverse clinical effects are observed [15]. Rivaroxaban is being used predominantly in prophylaxis of venous thromboembolism cases occurring following surgery as a postsurgical complication and also in cases in which venous thromboembolism is the primary and only diagnosis as a single drug therapy [21] [22] [23].

Treatment

The dosing schedule of rivaroxaban for the treatment of deep vein thrombosis and pulmonary embolism is 15 mg twice daily for 21 days followed by 20 mg once daily; the thrombus regression rates were high when the drug was administered twice daily [24]. The bleeding profile in once daily regimens was betterin rivaroxaban dosing regimen than twice-daily regimens over the 12-week treatment period. A decrease in the dosage from 20mg to 15mg once daily should be well-thought-out if the patient's risk of bleeding overshadows the risk of recurrent deep vein thrombosis and pulmonary embolism [23]. Rivaroxaban though is not recommended in patients with Creatinine Clearance of <15 mL/min [15]. Study conducted by the EINSTEIN investigators revealed rivaroxaban to be a very competent anticoagulant drug when used as a single drug approach in prophylaxis of deep vein thrombosis and pulmonary embolism when treated for 3,6 and 12months. Rivaroxaban had equal efficacy with respect to the primary outcome in cases of Deep vein thrombosis with 2.1% when compared with dual drug therapy of enoxaparin–vitamin K antagonist of 3.0% and hazard ratio of 0.68. The principal safety result was in 8.1% of the patients in each group [13] [17].In cases of pulmonary embolism Rivaroxaban had noninferior outcomes compared to standard therapy with the patients of rivaroxaban group having 2.1% against standard-therapy group 1.8% with hazard ratio of 1.12. The principal safety result occurred was 10.3% in patients with rivaroxaban group and 11.4% in those of the standard therapy group of patients [14] [17] [21] [22].

Uses as a Prophylactic Drug in**:**

1. Post abdominoplasty

Other studies also show that rivaroxaban can be used as a primary drug in prophylaxis of venous thromboembolism in cases of post abdominoplasty. Oral rivaroxaban when administered as a chemo prophylactic agent in post abdominoplasty patients was found to be safe along with low incidences of hematoma and symptomatic Venous thromboembolism formation on a dose of 10mg daily for 7days post operatively [24].

2. Post-orthopaedic procedures

Studies have also known to show rivaroxaban as a potent anticoagulating agent forprophylaxis in patients who underwent orthopaedic procedures like hip replacement, knee replacement, knee arthroplasty and other various orthopaedic procedures [25][26] [27]. These studies have indicated that use of rivaroxaban was as effective when compared to enoxaparin in prevention of post-operative symptomatic Deep Vein Thrombosis and Pulmonary Embolism[27]. The rate of occurrence of Deep vein thrombosis when comparing the effects of rivaroxaban with other drugs like enoxaparin was found that the patients treated with enoxaparin had an occurrence rate of 1.8% compared to 0.9% when the patients were treated with rivaroxaban and the rate of occurrence of Pulmonary embolism in the group of patients treated with enoxaparin was 0.7%compared to 0.3% in the rivaroxaban group.Rivaroxaban when given at a dose of 10 mg once daily was found to be superiorto enoxaparin given at 30mg twice daily a North American-approved dosage for the prevention of venous thromboembolism after total knee arthroplasty. Aprior trial,the RECORD3 study, showed thatrivaroxaban 10 mg once daily was alsosuperior when compared to enoxaparin given at theEuropean-approved dose of 40 mgonce daily for prevention of Venous thromboembolism aftertotal knee arthroplasty and other orthopaedic procedures [26][27]. The first dose of rivaroxaban which is around 10 mg can be usually given about 6-10 hours when the bleeding has ceased after the surgery; and can then be prescribed once daily. It is advisable to administer a complete course of 14 days' post Total Knee Arthroplasty and 35 days post Total Hip Arthroplasty [28] [29]. The paramount advantage of using rivaroxaban in such cases is that it does not requires the regular monitoring the coagulation status, such as PT and Partial prothrombin time (PTT). Moreover, its efficacy is not affected by meal intake, so it can be taken prior to or after meals. In a large research series, it has been found that the incidence of VTE was reduced to 49% in Europe and 31.4% in the United States, and the incidence is 70-79% lower than that recorded for enoxaparin and the incidence of bleeding is the same as that of enoxaparin[29].

3. Cancer patients

Cancer patients are highly prone to development of Venous thromboembolisms a phenomenon known as cancer associated Thrombosis. Rivaroxaban is found to have been emerging as an appealing substitute in treatment of cancer associated thrombosis due to the given fact that it can be taken orally which helps in

compliance and also rarely known clinically vital drug-to-drug interactions[30] [31] [32] [33].Numerous control trials have indicated rivaroxaban to be similarly effective as Vitamin-K antagonists for the prophylaxis of venous thromboembolism in patients suffering from cancer, with parallel rates of recurrence episodes and major bleeding complications. Nonetheless, these studies enrolled a limited amount of cancer patients and due to the details of their malignancies were not collected, adoption of rivaroxaban in clinical practice has been limited.

4. Pulmonary embolism

Based on clinical trials conducted no statistically significant differences in PE-related clinical outcomes between the rivaroxaban and standard of care cohorts, including recurrent venous thromboembolism (3.0% vs 5.3%; P=0.1793), major bleeding (2.0% vs 2.6%; P=0.6011), and death (2.5% vs 4.1%; P=0.2828), during follow-up. However, during the index hospitalization, the group prescribed rivaroxaban had a shorter mean index length of stay (6.3 vs 10.4days; P=0.0402), fewer patients experiencing at least one hospital acquired complications (10.3% vs15.9%; P=0.0506). Thus therefore indicating rivaroxaban having equal efficacy in prophylaxis and management of pulmonary embolisms[34] [35].

5. Post-DVT

A study conducted over risk for Venous Thromboembolism recurrence in Rivaroxaban-treated patients who continued versus discontinued therapy suggested thatpatientswith Venous thromboembolism who continued with prophylactic rivaroxabantherapyafterthe first 3-or 6-month treatmentperiodhada substantial decreased risk forVenous thromboembolism recurrencewithoutanincreased threat for major bleeding.These outcomes suggestthatgainsin efficacy observedinextended-therapytrials mayinterpret toclinicalpracticeandprovide provision for extended therapytocliniciansandpatients [36].

IV. Conclusion

Rivaroxaban as a single drug approach is a beneficial option for the prophylaxis of venous thromboembolism but is underutilised at this present time. The studies carried out so far like the EINSTEIN study do highlight their importance and efficacy as a single drugapproach in prevention of venous thromboembolism. Rivaroxaban hasbeen shown to be as equally effective the standard drugs in like low molecular weight heparin and vitamin k antagonists like warfarin in thromboprophylaxis with lower rates of recurrences and bleeding incidences with easy compliance as the drug is administered orally as compared to the other anticoagulants which are administered in patients via parenteral route. They also appear a better option than other available anticoagulants as they don't require frequent monitoring of coagulation parameters and are administered in fixed doses. Guidelines recommending their use are present. Incorporating this drug in daily hospital scenario needs work too and their usage differs from hospital to hospital and patient to patient. Even though the results of present clinical trials andstudies show significant evidence of their efficacy and compliance, further studies should be carried out to obtain a better insight of their prophylactic efficiency and a model needs to be articulated to ensure their effective implementation.

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