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BETRIXABAN – THE FIRST AND ONLY ORAL ANTICOAGULANT APPROVED FOR VTE

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ABSTRACT

Venous Thromboembolism (VTE) is one of the leading causes of preventable death. Though many drugs are already available for the treatment, all of them were non-oral with severe toxicities in renal and hepatic impaired patients. Betrixaban is a factor Xa inhibitor, orally active drug with unique characteristics like long Half-life, minimal renal excretion, minimal hepatic metabolism. This article provided review on all aspects of Betrixaban including its mechanism of action, its pharmacokinetics, pharmacodynamics, pre-clinical studies, clinical phases of this drug with a note on its safety and efficacy concerns on every phase and comparison with other existing treatments for VTE like Enoxaparin, Warfarin, and the emergence of extended duration thromboprophylaxis and its antidote Andexanet alfa.

KEYWORDS: Betrixaban, venous thromboembolism, clinical phase, safety and efficacy.

INTRODUCTION

Venous thromboembolism which includes Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE) or both is one of the leading causes of preventable death in hospitalized patients.[1,2,3,4,5] Deep vein thrombosis (DVT) is a condition in which a blood clot develops in the deep veins, most commonly in the lower extremities.[6] A part of the clot can break off and travel to the lungs, causing a pulmonary embolism (PE), which can be life threatening. It is also a major cause of morbidity, mortality (circulatory diseases secondary to myocardial infarction and stroke), Disability-Adjusted Life Years (DALY) and increased healthcare expenditure. Incidence of VTE is about 1/1000 persons/yr. This incidence rate increases with age in those who are over 80 years to about 5/1000.[1,2,3,4,5] Among symptomatic VTE patients, 1/3rd represents PE and the rest with DVT.[3] In an retrospective Indian registry study 70% of the subjects with VTE were males. DVT events including PE, excluding PE and PE alone are 64%, 23% and 13% respectively The factors that play a key role in the onset of VTE includes a set of both acquired and hereditary risk factors. Acquired factors include hip or knee replacement, fracture, major surgery, congestive heart failure, respiratory failure, paralytic stroke, extended mobility, increasing age and hereditary factors include deficiency of some natural coagulation factors like protein C, protein S, antithrombin (AT) and blood group (non-O blood group).[7] Causes of VTE include increased age, orthopedic surgery, prostatectomy, prolonged bed rest, hyperthyroid disease, arthroscopy, Cushing syndrome, obesity, smoking, reduced physical activity, high prothrombin and drugs like oral contraceptives, postmenopausal hormones, chemotherapy and corticosteroids.[8]

VTE can be diagnosed by clinical probability assessment using either wells score, revised Geneva or simplified revised Geneva and can be combined with D-dimer levels, which is a degradation product of crossed linked fibrin blood clot. This preliminary diagnosis helps to understand whether the patient needs to be further diagnosed with noninvasive imaging techniques like compression ultrasonography, venous ultrasound, computed tomographic (CT) venography and pulmonary angiography.[2,7,9] Treatment includes use of either traditional or new generation anti-coagulants; though Unfractionated heparin (UFH) , low molecular weight heparin (LMWH) were the keystone in both VTE prevention and treatment but these are being substituted by non-vitamin K antagonist oral anticoagulants (NOAC) like Dabigatran, Rivaroxaban, Apixaban and Edoxaban.[5,7,10]

Betrixaban, developed by Portola Pharmaceuticals Inc. is a recent FDA approved drug in June 23, 2017 under the category Non vitamin-k Oral Anti-Coagulant (NOAC) for the prophylactic treatment of VTE in medically ill patients who are at risk of developing VTE. It is the first of its kind to be approved for extended duration prophylaxis of VTE in acute medically ill patients.

Betrixaban

Although effective treatment (unfractionated heparin, low molecular weight heparin and warfarin) were available for the prevention and treatment of VTE in acute medically ill patients for high-risk individuals, these drugs have well-known limitations. Hence another class of drugs namely direct thrombin inhibitors and direct factor Xa inhibitors were being developed and evaluated for the prevention and treatment of venous thromboembolism. Dabigatran, Rivaroxaban, Apixaban and Edoxaban are the 4 non-vitamin K antagonist oral anticoagulants that are at least as effective and as safe as warfarin for the treatment of VTE and prevention in medically ill patients. These drugs not only have the unique features of conventional drugs including rapid onset of action, and peak plasma levels within 3 hours of oral administration but also have the advantage of oral administration rather than parenteral, predictable pharmacology in contrast to warfarin, low unevenness in anticoagulation effect, fixed-dose regimen and less propensity for drug and food interaction making it one of the most common drug of choice for the treatment and prevention of VTE. As there are 4 NOACs already available, any additional new drug to be added to this category for the same use, the drug must possess some unique pharmacological properties that are better for patient care than existing drugs. Nevertheless, these drugs have short half-lives, great propensity to accumulate in severe renal and hepatic impaired patients and care must be needed if concomitant cytochrome P450 enzyme inducers or inhibitors are given. Betrixaban is a new NOAC with distinct pharmacological properties, having minimal renal excretion (could be used in renal failure patients), minimal hepatic metabolism (less propensity for drug-drug interactions) and long half-life (advantage of once-daily dosing).[5]

Betrixaban is derived from 1,N-(5-chloropyridin-2-yl)-2-(4-(N, N-dimethylcarbamimidoyl)-benzamido) benzamide, which is an anthranilamide- based compound with potent factor Xa activity. Although several selected compounds have been analyzed, they showed a high affinity towards hERG channel (human Ether-a-go-go-Related Gene), cardiac potassium ion channel that mediates cardiac repolarization. Delay in cardiac repolarization, QT prolongation and risks of life-threatening arrhythmias are associated with hERG inhibition and thus raise safety concerns. One such selected safe compound was methoxy-substituted compound 11, as it demonstrated least hERG channel binding, potent selective FXa inhibition following oral administration and safe and efficacious pharmacodynamic and pharmacokinetic profile in animal models.[11] The molecular weight of betrixaban is 452 Da.[11,13]

Mechanism of action

Betrixaban is a novel, site-directed anticoagulant and potent inhibitor of coagulation factor Xa (FXa). It exhibits very high specificity towards FXa i.e., 86,000 fold more than other coagulation enzymes and inhibits both free and prothrombinase factor Xa.[12,13] It binds competitively to FXa and exhibits its inhibitory activity.[15] Inhibition of factor Xa decreases TG and thrombus formation. In the coagulation cascade, factor Xa is responsible for the conversion of factor II prothrombin to factor IIa thrombin. Thrombin generally acts in 2 ways; one such mechanism is by inducing the conversion of fibrinogen to fibrin. And the other mechanism is by activating factor XIII to form stabilized fibrin clots. And hence inhibition of Factor Xa by betrixaban prevents the above mechanism and is useful in preventing clot formation.[13]

Dose

Betrixaban is administered in a loading dose of 160 mg as the first dose followed by 80 mg once daily for a period of 35-42 days. In patients with severe renal insufficiency of <30 ml/min and receiving concomitant strong P-glycoprotein inhibitors, the dose of betrixaban is reduced to 40mg.[14]

Pharmacokinetics

Absorption

Betrixaban is rapidly absorbed with mean peak plasma concentrations occurring 3-4 hours after drug administration.[15,16]

Oral bioavailability

Oral bioavailability of an 80 mg dose betrixaban is around 34%.[15]

Effect of food

When people in fasting state and people who had taken high fat and high-calorie rich breakfast were compared, the later had Cmax and Area Under the Curve (AUC)reduced by 50%.[15]

Clearance

Clearance of Betrixaban is primarily through biliary excretion via the hepatobiliary route through P-glycoprotein efflux pump, mostly in unchanged form.[12,15] Nevertheless, as the drug depends majorly on the hepatobiliary system, there are greater chances for the drug to get accumulated in case of obstructive Jaundice.[5]

Distribution

About 60% of the drug is protein bound.[15] Betrixaban being a substrate for efflux proteins, concomitant use of potent P-glycoprotein inhibitors like ketoconazole, amiodarone, diltiazem, e.t.c., will result in a 2 fold increase in betrixaban levels[15,16] and more chance of drug-drug interactions.[5]

Metabolism

Only about 1% of the drug gets metabolized by CYP450 enzymes (Betrixaban does not act as a substrate for major CYP enzymes) and hence has reduced or lack of

potential for interactions with drugs that are metabolized with CYP450 enzymes (limited metabolism).[5,12,15]

Excretion

Only about 5%-7% of the orally administered betrixaban dose gets excreted in urine (minimal renal excretion), being the least renal excreted drug among all other approved NOACAs.[5,12]

Half life

The terminal half-time (time taken to get about 50% reduction in drug concentration) and pharmacodynamic half-life (time taken to get about 50% reduction in efficacy) are 37 hours and 20 hours respectively; demonstrates a low peak-to-trough concentration ratio.[5,15] The 20-hour pharmacodynamic half-life of this drug is accompanied by little diurnal variation in drug concentration and hence anti-FXa activity.[12]

Betrixaban vs Other Noacs

As previously stated ,betrixaban is superior to other NOACs in terms of least renal clearance, least hepatic metabolism, most gastrointestinal clearance and longest t1/2. Renal clearance of Dabigatran, Rivaroxaban, Edoxaban, Apixaban and betrixaban are 80%, 66%, 35%, 25% and 5%-7% respectively. By this data it is evident that betrixaban can be administered in renal impaired patients with creatinine clearance being about 30ml/min. Generally renal impaired patients would be eliminaed in clinical trials and the same scenario was for other NOAC trails. But in contrast to the above trails, betrixaban clinical trials had recruited subjects with renal impairment, as this drug has very limited renal excretion.[5]

Invitro and human plasma studies

In whole blood prothrombinase inhibition assay-invitro, betrixaban showed a dose-dependent inhibition of platelet-mediated prothrombinase activity. This is consistent with the drugs mechanism of action. When compared to fondaparinux, betrixaban was more potent in inhibiting thrombin-antithrombin (TAT) complex and F1+2 generation.[5,13] Betrixaban, in plasma concentrations that could range from 5ng/ml to 25ng/ml in a series of tissue factor-induced thrombin generation study inhibited thrombin generation in a way that could be achieved by S.C 2.5 mg fondaparinux.[5,12] Human plasma studies also demonstrate that betrixaban was more potent than fondaparinux in inhibiting thrombin-antithrombin (TAT) complexes and F1+2 generation at similar therapeutic concentrations.[13]

Preclinical studies

To demonstrate antithrombotic activity of betrixaban, 3 animal model studies were performed on rat carotid artery, rabbit vena cava and baboon arteriovenous (AV) shunt. In the rabbit abdominal vena cava model, betrixaban and enoxaparin were compared in respect to inhibitory activity on thrombus mass. Betrixaban and Enoxaparin were used in doses 3mg/kg and 1.6 mg/kg respectively. Both the drugs had nearly equal inhibitory activity i.e, 76% vs 96% inhibition. Unlike rabbit abdominal vena cava model, the rodent carotid artery model compared the efficacy of betrixaban not only with Enoxaparin but also with clopidogrel in doses being 19.1 mg/kg, 7.6mg/kg and 3mg/kg/day. These drugs showed similar activity with thrombus mass inhibition being 90% vs 70% vs 80% respectively. The specificity of rat and rabbit models on Factor Xa activity is less when compared to baboon model. Hence the prediction of required therapeutic plasma levels was as such with results of baboon model. In this model, Betrixaban when used in doses between 0.05 and 0.49 mg/kg, there was dose-dependent inhibition of venous thrombosis and hence anti-thrombotic activity.[5,12,13]

Ex vivo caogulation testing

To measure the anti-coagulant activity of betrixaban, various ex-vivo coagulation tests were performed both in animal and human plasma. Few clotting tests like prothrombin time (PT), activated partial thromboplastin time (aPTT) and activated clotting time (ACT) were comparatively insensitive and showed inter-species differences in betrixaban response. PT doubling in humans would occur at concentration of about 180 ng/Ml, whose concentration is far above the therapeutic betrixaban concentration 5-25ng/Ml. This is evident from the data that rat, rabbit, baboon and human plasma would attain PT doubling at 8.9 μM, 1.6 μM, 1.0 μM, and 0.4 μM concentrations respectively. Hence, it is not likely that betxixaban could affect PT time at therapeutic doses.[5]

Clinical Studies

Phase I Study

Phase 1 dose-escalation study of betrixaban was performed in 64 healthy individuals and had been well tolerated in wide dose ranging from 30-80 mg that would result in plasma levels for a therapeutic target range. The drug showed good oral bioavailability (47%), long elimination t1/2 of about 19hours, minimal renal excretion and a low potential to drug-drug interactions and hence could be used once daily without any need for dose adjustment in patients with altered renal function.[12,13,17]

Phase II(a) (EXPERT study)

Betrixiban vs enoxaparin

EXPERT study is a multicentre, randomized study where the subjects were randomized to take either one of the two doses of oral betrixaban or subcutaneous Enoxaparin. The study is double blinded where both the physicians and patients were blinded to betrixaban doses but not to Enoxaparin vs Betrixaban groups. The total sample size was 214. Men and women aged between 18 and 75 years who were undergoing Total Knee Replacement surgery were included in the study. Subjects with a very high risk of bleeding, recent history of bleeding events, low hemoglobin levels were exluded from the study. Medically ill patients undergoing Total

Knee Replacement (TKR) are at a higher risk of developing VTE. Hence patients who underwent unilateral TKR were randomized to receive either one of the two oral betrixaban doses (15 mg and 40 mg) twice daily or subcutaneous Enoxaparin (30mg) every 12 hours in a 2:2:1 ratio for a period of 10-14 days.

Efficacy
Primacy efficacy outcome is the occurrence of VTE up to 10 – 14 days post unilateral total knee replacement. VTE includes either the occurrence of proximal or/and distal DVT of the operated leg, symptomatic proximal DVT or Pulmonary Embolism.

After the standard therapy, the occurrence of venous thromboembolic events in betrixaban 15mg, betrixaban 40mg, and Enoxaparin 30 mg groups were 20%, 15.4%, and 10% respectively. 2 events of symptomatic DVT, one in 15mg betrixaban and one in 30 mg Enoxaparin group; 2 events of PE, one in betrixaban 15mg and one in betrixaban 40mg were seen. As predicted in earlier studies, this study also supports that the required therapeutic plasma concentration of betrixaban to be around 5-25ng/ml for effective treatment.

Efficacy of betrixaban was noted both in terms of TG inhibition and anti-Xa activity. Where, the inhibitory effect on TG of betrixaban 40mg was more distinct when compared to Enoxaparin 30mg. Both betrixaban 15mg and Enoxaparin 30 mg had similar TG inhibition. The anti-Xa activity is similar with betrixaban 40 mg and Enoxaparin 30 mg and less with betrixaban 15mg. By this is evident that betrixaban shows dose-dependent and concentration-dependent effect on both TG inhibition and anti-Xa levels and either increasing the dose or using a loading dose may result in increased efficacy.

Safety
The primary safety outcome was classified as either major or clinically relevant non major bleeding. Bleeding is said to be major when the event is either fatal, involves vital/essential organs of the body, requires surgery or any procedure or bleeding index ≥ 2.0. bleeding index is the number of units of either packed red blood cells (RBC) or whole blood transfused plus the difference in hemoglobin values before the bleeding event and after the bleeding event has stopped. Throughout the study, betrixaban 15 mg treated group had no bleeding events, betrixaban 40mg treated group had 2 CRMB and Enoxaparin treated group had 1 major and 2 CRMB. There were no death events in either treatment groups. Other safety concerns like vital signs, clinical laboratory parameters, electrocardiogram and adverse events monitoring were normal.[12,15]

Phase II(b) (EXPLORE-Xa)
betrixiban vs warfarin:
EXPLORE-Xa is randomized, double blinded study, in which betrixaban doses were blinded but not the allotment to either betrixaban or warfarin. Patients with Atrial Fibrillation (arrhythmia) are at an increased risk of developing ischemic stroke. Male and female patients (≥18years) with either Atrial Fibrillation (AF) or Atrial Flutter and atleast one more risk factor for stroke was included in the study. Patients with active bleeding, history of bleeding events, history of either intracranial or intraocular or retroperitoneal bleeding in the last 6 months, renal impaired patients on hemodialysis (HD) was excluded from the study. Patients who are at an increased risk of developing ischemic stroke were randomized to take either betrixaban 40mg, 60mg, 80mg once daily or warfarin (to have a target INR of 2.0 -3.0) in a 1:1:1:1 ratio and the patients were followed up to a maximum of 329 days.

The primary outcome of the study was the time to the onset of either major or clinically relevant non major bleeding (CRNB) and the secondary outcome was the time to the onset of a bleeding event to the onset of either death, Myocardial Infarction, stroke or any other systemic embolism.

Efficacy
Decreased TG was seen in all doses of betrixaban 40mg, 60mg, and 80mg, but with 80mg a similar decrease in TG when compared with therapeutic warfarin with a target INR being 2.0-3.0 was seen. This effect is achieved at a therapeutic concentration being between 12 and 30ng/ml. In respect to D-dimer levels, all the betrixaban treatment groups had a similar decrease in D-dimer levels in comparison to therapeutic warfarin (INR 2.0–3.0).

Safety
A bleeding event is said to be major event when there is either ≥ 20 g/l decrease in hemoglobin levels or when ≥ 2 units of packed or whole blood is needed to be transfused or bleeding in vital organ(s) or area(s). A bleeding event is said to be CRNB either if the event doesn't to the above criteria or which may result in discontinuation of therapy/drug, which results in uneasiness to the patient and reduction in quality of life. Throughout the study, the rates of major or CRNM bleeding of betrixaban treated groups were numerically lower when compared to warfarin-treated group i.e., 1,5,5 vs 7. Betrixaban 40 mg had lower events when compared to 60 and 80 mg while betrixaban 60mg and 80 mg had almost similar events compared with warfarin. Betrixaban 40 mg group had 1 vascular death. the betrixaban 60mg group had 1 ischemic stroke. betrixaban 80mg treated group had 1 ischemic stroke. The warfarin-treated group had 1 vascular death. Serious adverse events in betrixaban 40, 60, 80mg and warfarin-treated groups were 9.4, 9.4, 8.7 and 9.4 respectively. Other than the bleeding events, betrixaban is associated with an increased rate of diarrhea (pooled betrixaban vs warfarin: 6.0 vs 0.8%). By this data, it is evident that betrixaban is both effective and at the same time safer with reduced bleeding risk when compared to warfarin.[15]

Extended duration thromboprophylactic studies

Medically ill patients are at increased risk of developing venous thromboembolism (VTE) after hospital discharge, in spite of a recommended 7-10 days of short duration thromboprophylaxis. These short duration antithrombotic agents (Low Molecular Weight Heparin (LMWH), Low dose unfractionated heparin, or heparin) when used in medically ill patients, could only reduce VTE events to around 50%.[18] Hence a new hypothesis has been proposed that requires extended-duration thromboprophylaxis for a period of 30 days. Those studies were ADOPT((The Apixaban Dosing to Optimize Protection from Thrombosis), MAGELLAN (The Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin) and EXCLAIM (Extended Prophylaxis for Venous Thrombo Embolism in Acutely Ill Medical Patients With Prolonged Immobilization).[16,18]

a. ADOPT trial is a randomized double blind, double dummy, placebo controlled trial. In this study, 6528 medically ill patients were randomized to receive either extended-duration thromboprophylaxis with Apixaban (2.5 mg twice daily for 30 days) or short-duration thromboprophylaxis with subcutaneous Enoxaparin (40 mg for 6 to 14 days) and both were followed by placebo for 30 days. Primary efficacy outcome was the occurrence of either asymptomatic proximal DVT or fatal or nonfatal PE, or death in respect to VTE. Primary safety outcome is the occurrence of either major bleeding or CRMB. Primary efficacy outcome for Apixaban and Enoxaparin was 2.71% and 3.06% respectively. Major bleeding events in Apixaban and Enoxaparin were 0.47% and 0.19% respectively. In this extended thromboprophylaxis study, Apixaban failed to demonstrate superiority both in efficacy and safety. Rather than that there was about 2.5% increase in major bleeding which resulted in failure of this extended duration thromboprophylaxis with Apixaban.[14,16,18,19,20]
b. MAGELLAN trial is a multicenter, randomized, double blind trial. In this study, 8101 medically ill patients were randomized to receive either extended-duration thromboprophylaxis with rivaroxaban (subcutaneous placebo for 10 ± 4 days once daily followed by and rivaroxaban 10 mg once daily for 35 ± 4 days) or short-duration thromboprophylaxis with Enoxaparin (S.C dose of40 mg for 10 ± 4 days followed by oral placebo once daily for 35 ± 4 days). Primary efficacy outcome is the occurrence of either asymptomatic proximal VTE or symptomatic VTE. The primary safety outcome is the occurrence of major bleeding and CRMB. Primary efficacy outcome of both the treatment groups i.e., Rivaroxaban and Enoxaparin was 2.7% vs. 2.7% at day10 and 4.4% vs. 5.7% at day 35 respectively. The primary safety outcome of Rivaroxaban and Enoxaparin was 2.8% and 1.2% respectively. In this study, although Rivaroxaban demonstrated a significant reduction in venous thromboembolic events when compared to Enoxaparin group, but due to greater events of CRMB and deaths, this study failed to demonstrate a clinical benefit.[14,16,18,20,21]
c. EXCLAIM trial is a multicenter, double blinded, randomized placebo controlled trail in which randomization is computer generated. In this study, 5963 ischemic stroke patients would initially receive a standard open-label Enoxaparin S.C 40 mg for 10±4 days. After 10±4 days of therapy, they are randomized and double blinded to receive either Enoxaparin 40mg or placebo for 28 days. Medically ill patient's ≥40 years of age with recently diminished mobility and with additional risk factors like history of VTE and cancer. VTE events observed in Enoxaparin extended duration prophylaxis and placebo was 2.4% and 8.0% respectively. Major bleeding events in Enoxaparin extended duration thromboprophylaxis and placebo was 1.5% and 0% respectively. In this study, although Enoxaparin demonstrated a significant reduction in venous thromboembolic events when compared to placebo, but due to an increase in major bleeding events, this study failed to demonstrate a clinical benefit.[16,20,22]

Phase III (APEX TRIAL)

It is evident that from the above discussion that no study had shown clinically beneficial effects both in safety and efficacy in implementing extended duration thromboprophylaxis in preventing VTE events. With a hope that at least betrixaban could be beneficial in preventing VTE events, APEX trial was performed. APEX trial is a double blind, double dummy, active-controlled and multinational. In this study, 3759 medically ill patients were randomized to receive either extended-duration thromboprophylaxis with oral betrixaban or subcutaneous Enoxaparin. Betrixaban treatment group received a loading dose of betrixaban 160 mg for the first dose followed by 80 mg once daily for 35 to 42 days initially followed by subcutaneous Enoxaparin placebo once daily for 10 ± 4 days. Enoxaparin treatment group received 40 mg Enoxaparin S.C once daily for duration of 10 ± 4 days initially followed by oral betrixaban placebo once daily for 35 to 42 days. Doses for patients with severe renal insufficiency (creatinine clearance ≥15 mL and <30 mL per minute) were adjusted so as to have a loading dose of 80 mg was followed by a maintenance dose of 40 mg once daily for betrixaban and 20mg for Enoxaparin. Doses for patients who are receiving a concomitant strong P-gp inhibitor were adjusted so as to have a loading dose of 80 mg was followed by a maintenance dose of 40 mg once daily for betrixaban and the dose of Enoxaparin remained unchanged i.e., 40mg. Cohort 1 includes patients with D-dimer ≥2× upper limit of normal (ULN). Cohort 2 includes patients with D-dimer ≥2× ULN or had an age of ≥75 years. Cohort 3- includes all randomized patients who took at least 1 dose of study

drug during the treatment duration. The safety and efficacy of full dose (80mg) vs reduced dose (40mg) was also assessed.[16,23]

Efficacy

Medical ill Patients were given both 40 mg and 80 mg betrixaban doses to check superiority of one over the other. Median concentrations of 80mg and 40mg betrixaban treated groups are 19ng/ml and 11ng/ml respectively. Primary efficacy outcome was the occurrence of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE or VTE related to death. The primary efficacy outcome in cohort 1 for 80 mg extended duration betrixaban and 40 mg Enoxaparin groups was 6.27% and 8.39% respectively. There was a prominent improvement in the betrixaban treatment group in terms of VTE events in cohort-1 when compared with Enoxaparin treatment group. As the cohort-1 included the subjects with abnormal D-dimer levels, the reduction in VTE events was most prominent in central D-dimer laboratory than local D-dimer laboratory. Not only in cohort-1, consistent and significant reduction in VTE events was also seen in both cohort-2 and cohort-3. Considering the symptomatic events, there was significant rate reduction in 80mg betrixaban extended prophylaxis than Enoxaparin in cohort-1 (1.71 vs 2.56) and the same goes for cohort 2 and 3. In contrast, 40mg betrixaban failed to show significant difference with Enoxaparin treated group.

Safety

Composite of major and CRMB in cohort-1 for 80mg betrixaban group and Enoxaparin was 2.74% and 2.03% (50 vs 37 events). In cohort-2 its 2.80% and 1.77% (76 vs 48 events) and for cohort-3 its 2.71% and 1.64% (81 vs 49 events). Composite of major and CRMB in cohort-1 for 40 mg betrixaban group and Enoxaparin was 4.55% and 1.45% (22 vs 07 events). In cohort-2 its 4.98% and 1.50% (34 vs 10 events) and for cohort-3 its 4.79% and 1.38% (35 vs 10 events). It is clearly evident that betrixaban (80mg and 40mg) when treated results in more bleeding events when compared to standard enoxaparin therapy.[23] But it is worthy to note that- Are all the bleeding events are harmful? reversible? irreversible? major? minor? Fatal? Nonfatal? Hence a sub study is done considering only fatal and irreversible events called APEX trial sub study.

Apex trial sub study

Prior to the APEX study, it was stated that, results of cohort II would be assessed only when the first cohort results were statistically significant and likewise the same goes for cohort III result analysis too. Generally, the entire population efficacy would be evaluated prior than subpopulation studies, but in contrast, subpopulation cohort-1 was assessed prior to the entire population. This is to represent superiority of the drug in the selected individuals. But it is notable that cohort-1 marginally failed to demonstrate superiority, but showed superiority in both cohort-2 and cohort-3. As the prior objective was slightly crossed the border, there was more controversy whether the drug would be FDA approved or not. But it is notable that there was the greater superiority of betrixaban when compared with Enoxaparin in the entire population. In order to demonstrate safety issues, an APEX trial substudy was conducted considering only fatal and irreversible events.

APEX trial sub study is a multicentre, randomized and double blind study. A post hoc and time-to-first event survival analysis of the APEX trial was conducted which considered only the fatal and irreversible events that the betrixaban 80 and 40 mg groups had experienced excluding minor and reversible events. Primary end point was the composite of all fatal and reversible ischemic and bleeding events. Nonfatal PE was not included in irreversible events as this may or may not result in lung tissue necrosis and hence analysis was done both including and excluding non fatal PE. In cohort-3, the composite of fatal and irreversible events including non fatal PE for betrixaban group vs Enoxaparin was 2.9% and 4.1% (109 vs 153 events) at day 42. For analysis excluding non fatal PE, the events were 2.7% and 3.6% (101 vs 136). There was a consistent decrease in composite event rates in betrixaban when compared to enoxaparin in all the 3 cohorts. Number Needed to Treat 1 VTE event by betrixaban extended duration thromboprophylaxis is 65. And this NNT was only 43 in cohort 1 with a Risk Reduction of about 2.3%. But, in controversy, there was no significant reduction in events among adjusted betrixaban dose groups i.e., 40mg when compared with enoxaparin. Overall, app. 30% reduction in fatal or irreversible ischemic or bleeding events was seen in extended duration betrixaban among hospitalized medically ill patients when compared to standard duration enoxaparin.[14]

Extended duration betrixaban vs standard duration enoxaparin in the post parenteral period

The safety and efficacy of extended duration betrixaban and standard duration S.C Enoxaparin during parenteral therapy was already discussed at phase III APEX trial. . Yet, as the concern rises regarding the safety and efficacy during the post parenteral period in medically ill patients. The primary efficacy was the incidence of symptomatic DVT, non-fatal PE, or death in respect to VTE. This study was done following discontinuation of standard Enoxaparin parenteral therapy (Enoxaparin arm) and discontinuation of placebo parenteral Enoxaparin therapy (betrixaban arm). After discontinuation, active betrixaban (betrixaban arm) and placebo betrixaban (Enoxaparin arm) were compared. Betrixaban treated group had decreased VTE events than Enoxaparin group in the post parenteral period. Use of extended duration thromboprophylaxis of betrixaban in the post parenteral period had reduced incidence of VTE when compared to parenteral enoxaparin in acute medically ill patients.[24]

Betrixaban – its effect on QT prolongation

Effect of betrixaban on QT prolongation was studied in 96 healthy volunteers who were randomly assigned to take a single dose of either therapeutic 80 mg dose or supratherapeutic 140 mg and measured in terms of individual heart rate corrected QT duration (QTcI). These results are compared with a positive control moxifloxacin 400 mg group and placebo with the help of Electrocardiogram recording at pre-dose and post-dose at 1,2,3,4,5,6,8,12,16 and 24 hours. The pre specified clinically significant change in ECG for betrixaban was >10ms. None of the post-dose betrixaban demonstrated an ECG >10ms and the results were consistent for moxifloxacin too. This supra therapeutic 140 mg betrixaban may result in a 10 times the plasma concentration achieved in Apex trial. Hence it is concluded that betrixaban is safe and well tolerated through ECG study.[25]

Antidote – Andexanet Alfa

The major drawback of NAOCs is the non-availability of an antidote to be used either at the toxic doses of a drug or during bleeding event that occurred during treatment of that drug. Andexanet alfa (AnXa) is a modified recombinant FXa derivative that binds with high affinity to direct FXa inhibitors. This drug seems to be promising and hence clinical trials are being done to know its effect as an antidote. One such effort is to study the effect of andexanet alfa in reducing blood loss in rabbits after being treated with betrixaban. In this rabbit laceration study, anesthetized rabbits were given betrixaban in an initial IV bolus at a dose of 1mg/kg followed by a 10 min IV infusion at the rate of 1mg/kg/hr. 5 AnXa doses were selected 0,15,35,75 and 125mg/kg and each dose group would be tested with a minimum of 6 rabbits in each group. 20 minutes after betrixaban administration, rabbits were administered with Andexanet alfa doses. 25 minutes after Andexanet alfa administration, both right and left lobes of rabbit's liver were lacerated with a total of about 10 incisions (1-cm each). To assess the levels of total and unbound betrixaban, Andexanet alfa and anti-Fxa activity; blood samples were collected prior to Andexanet alfa administration, 5 min post-Andexanet alfa and at the end of a 15 min bleeding period. It was found that subjects on betrixaban are at a 2-fold increase in blood loss when compared with control group and treatment with Andexanet alfa significantly reduced blood loss (82.5% in 35 mg group and greater than 90% in 75 and 125 mg treated groups) and no significantly reduced blood loss (52.4%) in 15 mg treated groups. The dose-dependent decrease in betrixaban plasma concentrations was seen at the end of 5 min Andexanet alfa IV infusion, more significantly at 125mg treated groups (98%). Significant and dose dependent reversal of Anti-FXa activity was seen at 35mg, 75mg and 125mg treated groups. Hence, Andexanet alfa could be a promising drug in situations where there is active visceral bleeding and could significantly reduce blood loss by greater than 80% at 35, 75 and 125mg dose.[26]

CONCLUSION

In the present scenario none of the Food and drug administration (FDA) approved oral drug is available for the prevention and treatment of venous thromboembolism. The other approved parenteral drugs have its own limitations. Betrixaban is a new oral factor Xa inhibitor that is recently approved by FDA for thromboprophylaxis for VTE. It possesses unique characteristics that differentiate this drug with other available drugs. And those features include least renal clearance, least metabolism, large T1/2 and approved to be used in renal impaired patients. This drug provides superiority over the standard parenteral Enoxaparin and Warfarin therapies at phase IIa and IIb respectively. This is the first and the only drug to be approved for the extended duration thromboprophylaxis of VTE. Even though there was a debate whether betrixaban would be FDA approved or not, owing to its safety at reduced fatal and reversible events in comparison to standard Enoxaparin parenteral therapy, FDA finally approved. One concern regarding betrixaban use is the non availability of an antidote. Andexanet alfa might be a promising antidote for betrixaban if it gets approved in clinical trials. Hence Betrixaban is considered to be a revolutionary drug that is both safe and effective for the treatment of VTE.

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