

Does Rivaroxaban have a fibrinolytic effect?

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Abstract

Aim

The study started from the observation of complete recanalization of thrombus in subjects with DVT treated with rivaroxaban after 1-2 weeks. Aim of this clinical-instrumental observational retrospective research is to evaluate clinically and by means of Echo color Duplex the fibrinolytic effect of Rivaroxaban in patients with recent and previous DVT.

Methods

We evaluated two populations of patients:

1st group: 27 patients males (range of age 50-73 years) with popliteal-femoral DVT (12 months before) treated with standard anticoagulant therapy. In this patients we found a complete superficial femoral recanalization and partial recanalization of the popliteal vein (30% of residual thrombus). The patients had normal creatinine clearance and liver function. The patients switched from warfarin to rivaroxaban for no compliance to warfarin.

2nd group: 19 patients (range of age 65-85 years) with previous popliteal-femoral DVT and complete common femoral veins recanalization (already know or

documented). The patients presented recent superficial femoral vein re-thrombosis (1 week before). The patients had normal creatinine clearance and liver function.

Results

1st group: we observed in all patients the complete recanalization of the popliteal veins.

2nd group: we observed in all patients the complete recanalization of the superficial femoral veins after 2 weeks of the therapy of Rivaroxaban and complete recanalization of the popliteal veins after 4 weeks. No adverse events for both groups were observed.

Conclusion

According to our results, we consider that Rivaroxaban could have a fibrinolytic effect not only on recent thrombus but also on organized thrombus with, as result, a complete recanalization of affected veins and consequent reduction of incidence of post-thrombotic syndrome saving the valves structure.

Keywords Acute venous thrombosis, re-thrombosis, DOACs, post-thrombotic syndrome, fibrinolysis

Introduction

The objectives of anti-coagulation are prevention of extension of the thrombus, avoidance of pulmonary embolism (PE), prevention of recurrence of VTE and ultimately the avoidance of post-thrombotic syndrome (PTS). Considerable progress in the treatment of deep-vein thrombosis (DVT) of the lower extremities was achieved with the development of direct non-vitamin K antagonists (DOACs) and fibrinolytic therapies. Rivaroxaban is an oral, direct factor Xa inhibitor that inhibits free and clot-bound

factor Xa and factor Xa in the prothrombinase complex. Preclinical studies demonstrated a potent anticoagulant effect of rivaroxaban in plasma as well as the ability of this agent to prevent and treat venous and arterial thrombosis in animal models. These studies led to an extensive phase I clinical development program that investigated the pharmacological properties of rivaroxaban in humans^{1,2,3}.

The pharmacodynamic effects of rivaroxaban (for example, inhibition of factor Xa and prolongation of

prothrombin time) were closely correlated with rivaroxaban concentrations in plasma⁴.

Rivaroxaban is indicated for the treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults. For the initial treatment of acute deep vein thrombosis, the recommended dosage of rivaroxaban is 15 mg twice daily for the first 21 days followed by 20 mg once daily for continued treatment and prevention of recurrence⁵⁻⁸.

During the treatment of the patients with DVT we observed the complete recanalization of thrombus after 1-2 weeks. We presented these results during some congresses and other authors reported the same observation.

Aim of this clinical-instrumental observational retrospective research is to evaluate clinically the fibrinolytic effect of Rivaroxaban in patients with recent and previous DVT, i.e. with re-thrombosis or organized thrombus.

Material and methods

We evaluated two populations of patients (see table I)

1st group: 27 patients (mean age 50-73 years) with previous popliteal-femoral DVT (max 12 months before) treated with standard anticoagulant therapy at long time for different reasons.

The patients switched from warfarin to rivaroxaban for no compliance to warfarin (frequent long distance travel with important jet-lag, no observation for the food, continuous change of INR values, no correct observance of dosages).

At the first observation (time 0) by means of echo duplex we found a complete superficial femoral recanalization and partial recanalization of the popliteal vein (with 30% of residual thrombus).

2nd group: 19 patients (mean age 65-85 years) with the same presentation of 1st group (previous popliteal-femoral DVT with the complete common femoral veins recanalization and partial popliteal recanalization and residual thrombosis of 30%, already known or documented) but with recent superficial femoral vein re-thrombosis (onset 1 week before).

In these patients we started with the treatment with rivaroxaban due to intolerance to low molecular weight heparin (L.M.W.H.) and no compliance to warfarin.

We treated all patients with 15 mg BID for 21 days followed by 20 mg OD of Rivaroxaban for 3 months. All patients had normal creatinine clearance and liver function.

Both groups were submitted to the clinical and echo duplex examination at time 0 and at 1,2,3,4 weeks and after 3 months during the DOACs treatment.

Results

1st group: we observed in all patients after 2 weeks the complete recanalization of the popliteal veins (previous thrombosis with 30% of residual thrombus).

2nd group: in the same way, we observed in all patients the complete recanalization of the popliteal veins (previous thrombosis) after 4 weeks and the complete recanalization of the recent thrombosis of the superficial femoral veins after 2 weeks of the therapy of Rivaroxaban.

No adverse events for both groups were observed.

Conclusions

Factor X has long been known to have a key role in hemostasis, and its activated form, factor Xa, has a significant function in the blood coagulation pathway because it catalyzes the production of thrombin, which leads to clot formation. Activation of factor X to factor Xa occurs through both the intrinsic and extrinsic pathways of the coagulation cascade. Factor Xa initiates the final, common pathway that results in thrombin activation via the prothrombinase complex. Early studies of naturally occurring factor Xa inhibitors indicated that targeting factor Xa could provide effective anticoagulation⁸. Selective inhibition of factor Xa produces antithrombotic effects by decreasing the generation of thrombin, thus diminishing thrombin-mediated activation of both coagulation and platelets without affecting the activity of existing thrombin^{9,10}.

In the paper of Garabon¹¹ Rivaroxaban was shown to decrease the rate of coagulation, which was decreased further at higher concentrations of thrombomodulin (TM). The presence of either thrombin activatable fibrinolysis inhibitor (TAFI) variant also seemed to decrease clot formation rate at higher levels of rivaroxaban and TM. At all concentrations of TM, TAFI-dependent resistance to fibrinolysis was attenuated by rivaroxaban. The effect of rivaroxaban was, however, greater for wild-type TAFI than for the T325I variant. In conclusion, rivaroxaban exhibits TAFI-dependent profibrinolytic effects that are influenced by the levels of TM and the by intrinsic stability of TAFIa. TM also affected the dynamics of coagulation. These findings suggest a role for the anatomical location of a procoagulant stimulus and plasma TM-altering disease phenotypes in the pharmacodynamics and a role for the T325I polymorphism in the pharmacogenomics of rivaroxaban.

	1 st group	2 nd group
Patients	27	19
Mean age	61,5 years	66,8 years
Range	50-73 years	65-85 years
Males/females	9/18	8/11
Onset of previous thrombosis	max 12 months	max 12 months
Onset of acute thrombosis	...	1 week
Complications	none	none
Adverse effects by rivaroxaban	none	none

Table I - Patients data subdivided by groups. Treatment: rivaroxaban 15 mg BID for 21 days followed by 20 mg OD for 3 months. BID - bis in die. OD - once a day.

Álvarez¹² also showed that Rivaroxaban also altered (>2 fold change) the expression of matrix metalloproteinase 2 and urokinase plasminogen activator (u-PA), but counteracted the FXa (9 nM)-induced up-regulation of several pro-inflammatory genes ($P < 0.05$) and FXa-enhanced platelet adhesion over human umbilical vein endothelial cells (HUVEC). Rivaroxaban increased u-PA protein expression in HUVEC supernatants and enhanced u-PA activity (up to 4 IU ng⁻¹ of u-PA). Rivaroxaban (1nM–1μM) showed a significant and dose-dependent positive effect on HUVEC growth that was inhibited by BC-11-hydroxibromide, an inhibitor of u-PA. Healing properties after a wound on HUVEC cultures, and fibrinolytic properties were also shown by rivaroxaban. Both effects were reversed by BC-11-hydroxibromide. Rivaroxaban enhanced viability, growth and migration of HUVEC, mainly by u-PA activation and upregulation, which also participate in the rivaroxaban-induced fibrinolytic activity at endothelial level. Rivaroxaban also protected from the pro-inflammatory effects of FXa on HUVEC. Altogether may improve endothelial functionality and could contribute to the cardiovascular benefits of rivaroxaban.

From the clinical point of view, the EINSTEIN investigators^{13,14} conducted a post-hoc subgroup analysis of the Einstein DVT trial (N=3449) to assess the impact of rivaroxaban therapy on the development of PTS. Kaplan-Meier survival analysis was performed to compare the cumulative incidence of PTS between the rivaroxaban and enoxaparin/VKA groups. They included 336 patients, 162 (48%) treated with rivaroxaban and 174 (52%) with enoxaparin/VKA. The cumulative PTS incidence at 60 months was 29% in the rivaroxaban group and 40% in the enoxaparin/VKA group. After adjusting for age, gender, body mass index, previous VTE, ipsilateral recurrent DVT, extent of DVT, idiopathic DVT, duration of anticoagulant

treatment, compliance to assigned study medication, elastic compression stocking use and active malignancy, the HR of PTS development for rivaroxaban was 0.76 (95% CI: 0.51-1.13). The investigators concluded that treatment of acute DVT with rivaroxaban was associated with a numerically lower but statistically non-significant reduction in risk of PTS compared with enoxaparin/VKA treatment.

Van Es¹⁵ confirms early clot regression in acute PE following 21 days of rivaroxaban in the 88% of patients with PE.

Many of the pharmacological effects of Rivaroxaban and other DOACs on cardiovascular system remain unexplored at this time. Since novel mechanisms might be involved in venous recanalization during rivaroxaban treatment, we might have to return from bedside to the bench (basic science) to understand these mechanisms. Additional data with the DOACs will emerge from basic science as well as prospective clinical trials, ultimately helping cardiovascular patients prevail over such severe diseases.

We consider that our results showed that Rivaroxaban could have a fibrinolytic effect not only on recent thrombus, as demonstrated from several trials, but also on organized thrombus with, as result, a complete recanalization of the previous residual thrombus. This action probably is due to the effect on remodeling of endothelium, considering that the organization of thrombus begins after adherence of the clot to the vessel wall, with formation of a thin lining of endothelial cells over its surface, followed by ingrowth of cells from the intima media and capillary buds into the thrombus.

Our data allow us to consider rivaroxaban as useful drug for reducing the incidence of post-thrombotic syndrome saving the valves structure.

It may be clinically relevant to identify the speed of clot resolution during anticoagulant treatment. As in patients with a suspected recurrent DVT, it is often unclear whether thrombi reflect a recurrence or an old thrombus. Consequently, knowledge about the time to clot resolution

might be helpful in the diagnostic work-up of patients with recurrent DVT. In our case reports, we observed the complete resolution of acute thrombi after 2 weeks and the complete recanalization of old thrombi after 4 weeks.

Of course, it is necessary more observation to confirm these hypotheses and to establish the correct dosage of drug but probably the single drug approach (20 mg OD) at long time could be the correct treatment.

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