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CAN THE TREATMENT OF DVT WITH RIVAROXABAN REDUCE THE INCIDENCE OF POSTTHROMBOTIC SYNDROME?

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The study was initiated following observation of complete recanalization of thrombus in subjects with DVT treated with rivaroxaban after 1–2 weeks.
The aim of this observational retrospective study was to evaluate clinically, and by means of Echo color Duplex, the fibrinolytic effect of rivaroxaban in patients with recent and previous DVT. To this end, we evaluated two populations of patients:
1st group: 31 patients (range of age 52–73 years) with popliteal-femoral DVT (12 months ago) treated with standard anticoagulant therapy (warfarin). In these 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 were switched from warfarin to rivaroxaban due to a lack of compliance with warfarin therapy.
2nd group: 22 patients (range of age 65–82 years) with previous popliteal-femoral DVT and complete common femoral veins recanalization (already known or documented) who presented with a recent superficial femoral vein re-thrombosis (1 week before). The patients had normal creatinine clearance and liver function. The patients switched from warfarin to rivaroxaban due to a lack of compliance with warfarin therapy.
Results. In the 1st group, all patients exhibited the complete recanalization of the popliteal veins after 4 weeks of rivaroxaban therapy. In the 2nd group, all patients exhibited the complete recanalization of the popliteal veins after 4 weeks, and the complete recanalization of the acute re-thrombosis of the superficial femoral veins, after 2 weeks of rivaroxaban therapy. No adverse events for both groups were observed.
Our results suggest that rivaroxaban could have a pro-fibrinolytic effect not only on recent thrombus but also on organized thrombus that results in a complete recanalization of affected veins. It is proposed that this lytic effect will preserve venous valve structure and lead to a reduction of incidence of post-thrombotic syndrome in treated patients.

Keywords: *rivaroxaban, DVT.*

Introduction. In patients receiving anticoagulation for the treatment of thrombosis, the goals of therapy 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). Post-thrombotic syndrome i sa problem that can develop in nearly half of all patients who experience a deep vein thrombosis (blood clot) in the leg. PTS symptoms include chronic leg pain, swelling, redness, and ulcers (sores). PTS has been estimated to affect 23–60 % of individuals with DVT, frequently occurring within 2 years of the DVT episode. Among factors potentially related to the development of PTS is the lack of vein recanalization within the first 6 months following. Clearly, earlier, more complete recanalization correlates with less PTS [1–2].

Rivaroxaban is a direct oral anticoagulant that specifically targets factor Xa. The pharmacodynamic effects of rivaroxaban (for example, inhibition of factor Xa and prolongation of prothrombin time) are closely correlated with rivaroxaban concentrations in plasma [4]. Rivaroxaban is approved for a variety of indications including the treatment of acute DVT. 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 recurrence [3–7]. There has been the suggestion in the literature that rivaroxaban administration may be associated with additional

effects beyond anticoagulation. For instance, during the treatment of the patients with DVT, a complete recanalization of thrombus has been observed following 1–2 weeks of rivaroxaban therapy [8].

The aim of the current observational retrospective research is to evaluate clinically the fibrinolytic effect of rivaroxaban in patients with recent and previous DVT.

Material and methods. Two populations of patients were evaluated in this study. Group 1 consisted of 32 patients with a mean age of 60.7 years (range 52–73 years), whose previous popliteal-femoral DVT (12 months ago) was treated with standard anticoagulant therapy (warfarin). These patients experienced complete superficial femoral recanalization, but only partial recanalization of the popliteal vein. These patients had a mean residual thrombus of 30 % in the popliteal vein. Group 2 consisted of 22 patients with a mean age of 64.5 years (range 65 to 82 years) with previous popliteal-femoral DVT and complete common femoral veins recanalization with partial recanalization of the popliteal vein (already known or documented) who also experiences a recent superficial femoral vein re-thrombosis (1 week before). Patient demographics are described in Table 1.

At the time of enrollment, patients were switched to rivaroxaban due to a lack of compliance with warfarin therapy (frequent long distance travel with important jet-lag, no observation for the food, continuous change of INR values, no correct observance of dosages) or an intolerance to warfarin. Patients in both groups were treated with standard dosages of rivaroxaban, 15 mg twice daily for the first 21 days followed by a 20 mg once daily. All patients had normal creatinine clearance and liver function. All patients underwent clinical and echoduplex examination prior to initiating rivaroxaban therapy and every 7 days during rivaroxaban treatment.

Table 1

Populations of patients evaluated in the study

	Group 1	**Group 2**
Patients	32	22
Mean age	60.7 years	64.5 years
Range	52–73years	65–82 years
Males/females	11/21	10/12
Onset of old thrombosis	max 12 months	max 12 months
Onset of acute thrombosis	-	1 week
Complications	none	none
Adverse effects by rivaroxaban	none	none

Results and discussion. Figure 1 shows by duplex ultrasound the recanalization of the popliteal vein following 4 weeks of treatment with rivaroxaban. All patients in group 1 exhibited complete recanalization of the popliteal veins after 4 weeks of treatment with rivaroxaban. In group 2, all patients exhibited complete recanalization of the popliteal veins after 4 weeks as well as the complete recanalization of the acute re-thrombosis of the superficial femoral veins after 2 weeks of the therapy of rivaroxaban. No adverse events for both groups were observed.

Factor X has long been known to have a key role in hemostasis. 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 anticoagulation [9]. 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 [10–12].

Rivaroxaban has been shown to decrease the rate of coagulation, which was decreased further at higher concentrations of thrombomodulin (TM) [13]. The presence of either thrombin activatable fibrinolysis inhibitor (TAFI) or its T325I 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. Thus, it appears that 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.

It has been shown that rivaroxaban administration produces a>2 fold increase in the expression of matrix metallopeptidase 2 and urokinase plasminogen activator (u-PA), and prevents the FXa (9 nM)-induced up-regulation of several pro-inflammatory genes and FXa-enhanced platelet adhesion to human umbilical vein endothelial cells (HUVEC). Rivaroxaban increased u-PA protein expression in HUVEC supernatants and enhanced u-PA activity. Rivaroxaban ($1\ nM^{-1}\mu M$) produced a significant, dose-dependent positive effect on HUVEC growth that was inhibited by BC-11-hydroxybromide, an inhibitor of u-PA. Healing properties after a wound on HUVEC cultures, and fibrinolytic properties were also observed following rivaroxaban exposure.

Both effects could be reversed by BC-11-hydroxybromide. Rivaroxaban enhanced viability, growth and migration of HUVEC, mainly by u-PA activation and upregulation, which also contributes to the rivaroxaban-induced fibrinolytic activity of the endothelium. Rivaroxaban also protected HUVEC from the pro-inflammatory effects of FXa. Altogether, these results suggest a means by which rivaroxaban may improve endothelial functionality and provide cardiovascular benefits.

Some laboratory tools for determining the rate of thrombus formation and fibrinolysis in whole blood and plasma include techniques such as the thromboelastograph (TEG) and an assay performed in a 96-well microtiter plate (MPA). As reported by Lau et al (15) the rate of clot dissolution is more rapid in rivaroxaban patients. The TEG and MPA identify differences in thrombogenesis and fibrinolysis in the presence of different DOACs with major action in rivaroxaban patients. Rivaroxaban had the greatest influence of slowing thrombogenesis, giving a result (69 % inhibition) close to that of warfarin (65 % inhibition).

From the clinical point of view, the EINSTEIN investigators [16, 17] 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 in rivaroxaban and enoxaparin/VKA-treated 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 as signed study medication, elastic compression stocking use and active malignancy, the hazard ratio for PTS development with rivaroxaban treatment 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 Es [18] confirms early clot regression in acute PE in the 88 % of patients with PE following 21 days of rivaroxaban.

Koitabashi [19] reported a case of a 77-year-old patient with a proximal deep-venous throm-

bosis (DVT) with external compressive syndrome (such as May-Thurner Syndrome) who experienced a substantial reduction of thrombus mass. The patient was enrolled in the J-EINSTEIN Study (the Japanese EINSTEIN VTE treatment with rivaroxaban program) and was assigned to receive rivaroxaban 15 mg twice daily for 21 days, the initial therapy on-label regimen. His leg edema progressively decreased. CT scan on day 22 showed that the iliac vein thrombosis had almost completely disappeared.

These data were supported by another small study conducted by Kusnetzov [20]. In evaluating 33 DVT patients treated with rivaroxaban (15 mg BID for 3 weeks followed by 20 mg OD) and 38 patients treated with enoxaparin followed by VKA, significant vein reopening detected by duplex scanning was observed in the group treated with rivaroxaban. Interestingly, it was observed that such recanalization happened in the early stages of treatment, when rivaroxaban was being administered at a dose of 15 mg BID. No major bleeds were reported in either arm.

Our results indicate that rivaroxaban could have a fibrinolytic effect not only on the recent thrombus, as demonstrated from several trials, but also on organized thrombus with a complete recanalization of the previous residual thrombus. This action may be due to an effect on remodeling of the 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 suggest that rivaroxaban could be a useful drug for reducing the incidence of post-thrombotic syndrome and preservation of the valve 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.

While additional observations to confirm these hypotheses and to establish the correct dosage of drug are necessary, we believe that the single drug approach (20 mg OD) for extended periods could be the correct.

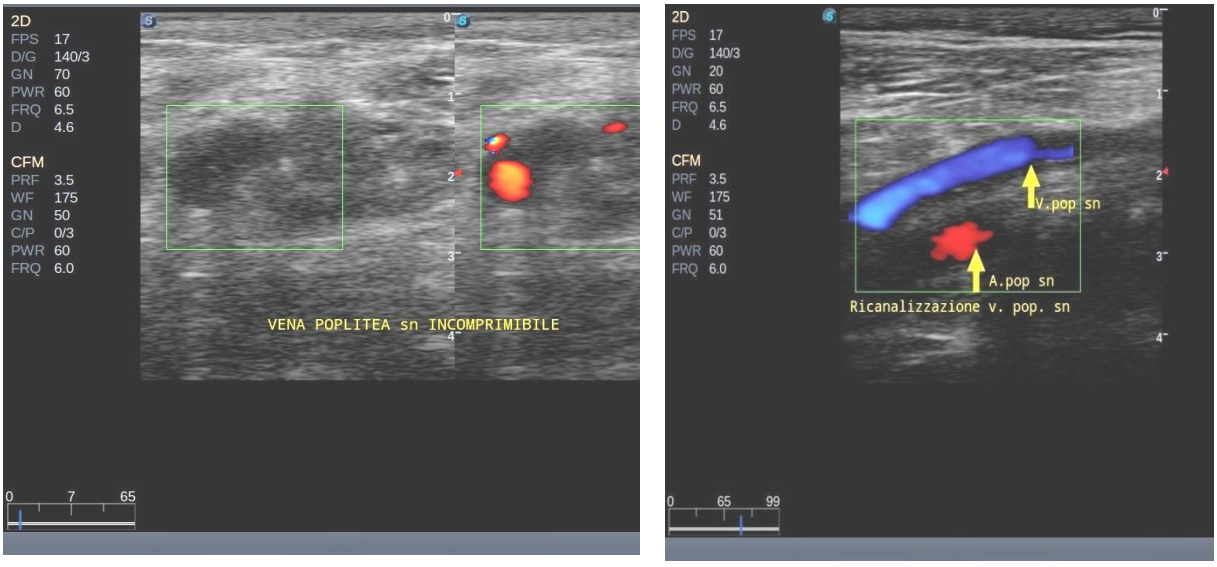

Fig. 1. Previous thrombosis of popliteal vein (a) and recanalization after 4 weeks of treatment (b)

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СНИЖАЕТ ЛИ ИСПОЛЬЗОВАНИЕ РИВАРОКСАБАНА ПРИ ЛЕЧЕНИИ ТРОМБОЗА ГЛУБОКИХ ВЕН ЧАСТОТУ ВОЗНИКНОВЕНИЯ ПОСТТРОМБОТИЧЕСКОГО СИНДРОМА?

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Исследование проводилось после выявления полной реканализации тромба у пациентов с тромбозом глубоких вен (ТГВ), получавших ривароксабан через 1–2 нед.

Цель этого экспериментального ретроспективного исследования состояла в том, чтобы оценить клинически и с помощью цветной доплер-эхокардиографии фибринолитический эффект ривароксабана у пациентов с ТГВ и пациентов, перенесших ТГВ.

С этой целью были сформированы две группы пациентов. Первую группу составил 31 пациент (52–73 года) с ТГВ подколенно-бедренной локализации (перенесенным 12 мес. назад), получавший стандартную антикоагулянтную терапию (варфарин). У этих больных была обнаружена полная поверхностная реканализация бедра и частичная реканализация подколенной вены (30 % остаточного тромба). Клиренс креатинина и функция печени у данных пациентов были в норме. Пациенты были переведены с варфарина на ривароксабан из-за несоблюдения терапии варфарином. Вторая группа была представлена 22 больными (65–82 года) с ТГВ подколенно-бедренной локализации и полной реканализацией общих бедренных вен (документально подтвержденной). У пациентов данной группы неделей ранее был повторно диагностирован поверхностный тромбоз бедренных вен. Клиренс креатинина и функция печени также были в норме. Пациенты перешли от варфарина к ривароксабану из-за несоблюдения терапии варфарином.

Результаты. У всех пациентов первой группы обнаружена полная реканализация подколенных вен после 4 нед. терапии ривароксабаном. Во второй группе у всех пациентов выявлена полная реканализация подколенных вен через 4 нед. и полная реканализация острого ретромбоза поверхностных бедренных вен через 2 нед. после терапии ривароксабаном. Никаких побочных эффектов в обеих группах не наблюдалось.

Заключение. Полученные результаты свидетельствуют о том, что ривароксабан может оказывать профибринолитическое действие не только на новый, но и на уже сформировавшийся тромб, что приводит к полной реканализации пораженных вен. Предполагается, что этот литический эффект сохранит структуру венозного клапана и приведет к уменьшению частоты посттромботического синдрома у пациентов, получавших соответствующее лечение.

Ключевые слова: *ривaксабан, тромбоз глубоких вен.*