Treatment of portal, mesenteric, and splenic vein thrombosis with rivaroxaban.
A pilot, prospective cohort study

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Patients with splanchnic vein thrombosis are at increased risk of recurrent VTE and bleeding. Routine anticoagulation with unfractionated heparin or low molecular weight heparin followed by warfarin is recommended in this setting, but limited data...

Ethical review	Approved WMO
Status	Pending
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON48974

Source
ToetsingOnline

Brief title
RIVASVT100 Trial

Condition

- Embolism and thrombosis

Synonym
abdominal vein thrombosis, Splanchic thrombosis

Research involving
Human

Sponsors and support

Primary sponsor: Università degli Studi dell'Insubria

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: effectivity, rivaroxaban, safety, Splanchic thrombosis

Outcome measures

Primary outcome

Primary Outcome of the study is the occurrence of major bleeding events during the 3 months of active treatment and up to 2 days after the end of study treatment.

Secondary outcome

Secondary outcomes include:

o Mortality (overall and SVT related);

o Clinically relevant, non-major bleeding occurred during the 3 months of active treatment and up to 2 days after the end of study treatment;

o Detection of alanine aminotransferase levels of three times the upper limit of the normal range or higher with or without bilirubin levels of two times the upper limit of the normal range or higher during follow-up;

o Patency of the portal vein trunk and at least one of its main right or left branches and patency of the superior and inferior mesenteric veins and of the splenic veins, defined as the normal appearance of a previously obstructed segment (as opposed to *obstruction*, defined as the presence of solid material in the vascular lumen);

o Recurrent SVT, defined as thrombus extension or occurrence in a previously patent segment;

o Symptomatic VTE in other sites, as diagnosed by appropriate imaging tests

according to the site of thrombosis;

o Mesenteric infarction as evidenced by a pathology specimen.

Study description

Background summary

Splanchnic vein thrombosis (SVT) is an unusual site manifestation of venous thromboembolism (VTE). It includes the Budd-Chiari syndrome (BCS), portal vein thrombosis (PVT), mesenteric vein thrombosis (MVT) and splenic vein thrombosis (spVT). PVT is the most frequent manifestation of SVT, followed by MVT. Although accurate epidemiologic data are scant, the diagnosis of SVT is likely increasing also due to the larger use of abdominal ultrasound or computed tomography in at risk populations, such as patients with liver cirrhosis or solid abdominal cancer. In a recent retrospective review of all abdominal CT scans performed at a single institution, we reported 1.74% prevalence of incidentally detected abdominal vein thrombosis, mainly in the splanchnic venous system [1].

SVT is a potentially life-threatening disease, with a broad range of clinical presentations including abdominal infarction or gastrointestinal bleeding. Acute MVT is associated with intestinal infarction in almost one-third of patients and has a mortality rate of 20% at 30 days [2]; gastrointestinal bleeding and ascites can be found in up to one-fourth of patients with PVT and BCS, and are triggered by portal hypertension [3].

The complex balance between the increased bleeding risk associated with esophageal varices and thrombocytopenia and the thrombotic predisposition associated with cirrhosis and malignancy, among others, make the treatment of SVT a clinical challenge. Unfortunately, no randomized controlled trials are available and current recommendations are derived from observational studies with high risk of selection bias.

In the absence of major contraindications, anticoagulant therapy is generally recommended for all patients presenting with acute symptomatic SVT, starting with either low-molecular weight heparin (LMWH) or unfractionated heparin and continuing with the vitamin K antagonists in most patients [4]. Treatment of incidentally detected SVT is suggested only for patients with evidences of acute thrombosis, thrombus extension or concomitant risk factors for recurrence (e.g. concomitant cancer). As for usual site VTE, it is generally recommended that anticoagulant treatment should be continued for at least 3 months, or

indefinitely if underlying persistent prothrombotic factors are identified [4]. Very few data are actually available on the short- and long-term rates of recurrent SVT and bleeding and only very few studies have a sufficiently large sample size to provide some meaningful information. The only prospective study was a European multicenter study assessing the outcome of early anticoagulation after acute PVT [5]. Anticoagulant treatment successfully prevented thrombus extension and was associated with a favorable 1-year recanalization rate (38% for portal vein, 54% for splenic vein and 61% for superior mesenteric vein), two patients developed mesenteric infarction [5]. Bleeding was reported in nine of the 95 treated patients, but neither definition of the severity of this outcome nor the timing of the events was provided in the study. In a retrospective cohort of PVT patients, of whom nearly two thirds were treated with anticoagulant drugs, the incidence rate of thrombotic events was 5.5/100 patient-years and the absence of anticoagulant therapy was an independent predictor for thrombosis [6]. Gastrointestinal bleeding occurred with an incidence rate of 12.5/100 patients-year, but again no standardized definition of bleeding severity was used in this study [6].

We previously assessed the long-term safety and efficacy of anticoagulant treatment in a multicenter, retrospective cohort study on patients with MVT receiving secondary prevention with vitamin K antagonists (VKA) [7]. The overall recurrence rate was 2.34/100 patient-years and increased to 4.59/100 patient-years after discontinuation of treatment. The incidence of hemorrhagic complications was low, with only 2.6% of patients experiencing a major bleeding event [7].

In a recent prospective multicenter, international registry on more than 600 SVT patients, we observed that the majority of patients were initially treated with LMWH, and that more than a third of them were continued on long-term parenteral treatment [8].

Rivaroxaban has been approved by the European Medical Agency for the acute phase treatment and the long-term secondary prevention of deep vein thrombosis of the lower limbs and pulmonary embolism. In the Einstein studies, rivaroxaban was administered at the dosage of 15 mg twice a day for the first 3 weeks followed by 20 mg once daily in patients with acute DVT and was compared to the standard therapy with LMWH and VKA [9,10]. The primary outcome measure of symptomatic recurrent VTE was similar between the two groups as well as the incidence of bleeding events.

Study objective

Patients with splanchnic vein thrombosis are at increased risk of recurrent VTE and bleeding. Routine anticoagulation with unfractionated heparin or low molecular weight heparin followed by warfarin is recommended in this setting, but limited data is available to support this recommendation and more than 20% of these patients do not receive antithrombotic treatment due the fear for

bleeding complications.

The pharmacokinetic and pharmacodynamic characteristics of rivaroxaban make this drug an ideal alternative therapeutic strategy for the treatment of patients with SVT. Thanks to the oral route of administration, the short half-life, the high bioavailability, the predictable dose-response and the lack of effects on platelet activity, rivaroxaban could result as an important alternative to both LMWH and warfarin in the acute and long-term treatment of SVT patients. A few anedoctal experiences with rivaroxaban in this setting have recently been published [11].

Furthermore, in the pooled analysis of the EINSTEIN studies, the incidence of major bleeding was significantly reduced from 1.7% in the standard therapy group to 1.0% in the rivaroxaban group (hazard ratio 0.54; 95% CI, 0.37-0.79) [12], and this observed benefit in the safety profile of rivaroxaban would be extremely relevant in the treatment of patients with SVT, given their potential higher risk of bleeding as compared to patients with deep vein thrombosis in the lower limbs.

In this prospective cohort study, patients presenting with acute SVT will receive rivaroxaban 15 mg bid for 3 weeks followed by rivaroxaban 20 mg once daily for a total of 3 months. The primary safety and efficacy outcomes will be measured at 3 months.

Study design

This a Phase 3, Single Group Assignment, Open Label, prospective cohort study aiming to treat Portal, Mesenteric, and Splenic Vein Thrombosis With Rivaroxaban.

Intervention

Rivaroxaban 15 mg bid for three weeks followed by rivaroxaban 20 mg once daily for a total of 3 months. After the end of the study period the decision to continue anticoagulant treatment with any of the available drugs will be left to the discretion of the attending physician.

Study burden and risks

Rivaroxaban, like other anticoagulants, should be used with caution in patients with
an increased bleeding risk. Bleeding can occur at any site during therapy with rivaroxaban. The possibility of a hemorrhage should be considered in evaluating the condition of any
anticoagulated patient. Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site. Certain medications may increase

the bleeding risk. Please refer to the concomitant medications section for further details (section 3.3).

Should severe bleeding occur, treatment with rivaroxaban must be discontinued and the
source of bleeding investigated promptly. Close clinical surveillance (looking for signs of bleeding or anemia) is recommended throughout the treatment period, especially in the presence of multiple risk factors for bleeding (see Table 1 below).

Table 1 - Factors Which Increase Hemorrhagic Risk

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients aged 18 years or older
2. First episode of symptomatic, objectively diagnosed PVT, MVT, or spVT (diagnosed by CT, MRI and/or Doppler ultrasound).
3. Signed informed consent.

Exclusion criteria

1. Known liver cirrhosis (biopsy proven or with clinical, laboratory, or imaging evidence of chronic liver disease, within a context of chronic alcoholism, viral hepatitis, autoimmunity, Wilson's disease, iron overload)
2. Alanine aminotransferase level that is three times the upper limit of the normal range or higher
3. Budd-Chiari syndrome
4. Previous or ongoing variceal bleeding
5. Presence of portal vein cavernoma at the time of diagnosis
6. Anticipated abdominal surgical procedure
7. Known bleeding diathesis
8. Platelet count <100.000 mm3
9. Creatinine clearance <30 mL/min (Cockroft-Gault formula)
10. Life expectancy of less than 3 months
11. Expected inability to take oral medications
12. Concomitant treatment with azole antimycotics and human immunodeficiency virus protease inhibitors
13. Treatment with therapeutic doses of LMWH or UFH for more than 7 days
14. Ongoing treatment with Vitamin K Antagonists (VKA)
15. Pregnancy or lactation.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	02-09-2019
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Rivaroxaban
Generic name:	Xarelto
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-06-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-005162-29-NL
ClinicalTrials.gov	NCT02627053
CCMO	NL67125.018.19