Resolution Enhancement by a Supplemental Open-Label Venoactive drug for Eight weeks in Deep Vein Thrombosis

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

Summary

ID

NL-OMON52521

Source
ToetsingOnline

Brief title
The RESOLVE-DVT study

Condition

- Embolism and thrombosis

Synonym
Deep vein thrombosis

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht

Source(s) of monetary or material Support: Ministerie van OC&W,ZonMw,Trombosestichting Nederland

Intervention

Keyword: deep vein thrombosis, flavonoid, post-thrombotic syndrome, residual venous obstruction

Outcome measures

Primary outcome

Presence of RVO in proximal venous segments determined by echography at 12 weeks after DVT.

Secondary outcome

Levels of circulating makers (e.g. hs-CRP, IL-6, IL-8, IL-10, TNF-α, ICAM-1, VCAM-1, P-selectin, FVIII, MMP-1, MMP-8) at baseline, 1 week, 4 weeks, 8 weeks and 12 weeks after DVT.

Scores on PTS-characterizing clinical signs of the affected leg (circumferences, pitting-edema, hyperpigmentation, venous ectasia, redness, skin induration, pain during calf compression, venous ulcers) at baseline, 1 week, 4 weeks, 8 weeks and 12 weeks after DVT.

Scores on PTS-characterizing symptoms of the affected leg (pain, cramps, heaviness, paresthesia, pruritus) at baseline, 4 weeks and 12 weeks after DVT.

Scores on quality of life at baseline, 4 weeks and 12 weeks.

Study description

Background summary

One in three patients experiences chronic signs and symptoms in the affected leg after deep vein thrombosis (DVT). This is referred to as the post-thrombotic syndrome (PTS). Current prevention of PTS is limited to elastic compression therapy (ECT) in the acute phase of the DVT. Considering the major societal burden associated with PTS, supplementation of current prevention with an effective pharmacotherapeutic therapy could be of high value. Since the pathogenesis of PTS is mediated through inadequate thrombus resolution damaging the vessel wall and increasing inflammation, the venoactive flavonoids with their vasoprotective and anti-inflammatory effects provide an excellent candidate. As an investigational medicinal product (IMP), the highly effective flavonoid O-β-hydroxyethylrutoside (HR) was chosen.

Study objective

The central question of this study is *What is the effect of supplementation of regular therapy with 8 weeks of HR after a first, acute, proximal DVT of the lower extremity on objective aspects of thrombus resolution which are associated with the development of PTS?*

To address this aim, the following objectives were formulated:

Primary objective
* What is the effect of additional HR treatment for 8 weeks in combination with regular therapy on RVO after an acute, proximal DVT of the lower extremity?

Secondary objectives
* What is the effect of additional HR treatment for 8 weeks in combination with regular therapy on PTS-associated circulating biomarkers after a first, acute, proximal DVT of the lower extremity?

* What is the effect of additional HR treatment for 8 weeks in combination with regular therapy on PTS-characterizing symptoms and clinical signs after a first, acute, proximal DVT of the lower extremity?

* What is the effect of additional HR treatment for 8 weeks in combination with regular therapy on quality of life after a first, acute, proximal DVT of the lower extremity?

Study design

This pilot study is designed as a single-center, open-label, randomized,

controlled, clinical trial. It will recruit patients who present themselves at the emergency department (ED) with a first, acute, proximal DVT of the lower extremity that has been objectively confirmed. Upon inclusion, patients are randomly allocated evenly between the intervention or control group. Patients in the intervention group receive treatment with HR for 8 weeks, the duration of thrombus resolution, and starting within 48 hours after diagnosis of DVT. Since the outcome measures are objective, there is no need for a placebo medicine in the control group. All patients receive regular treatment, consisting of ACT and ECT in accordance with the latest guideline on antithrombotic therapy by the Dutch internist association. During a follow-up period of twelve weeks, patients are seen five times: on baseline (<48h after diagnosis of DVT) and after 1 week, 4 weeks, 8 weeks and 12 weeks at the outpatient clinic. At all these visits, secondary outcomes are measured by anamnesis, blood drawing and assessment of the affected leg. At the last visit, the primary outcome measure is determined by echography. Visits at 4 and 12 weeks and echography can be combined with the regular clinical care pathway.

Intervention

Investigational treatment
Patients in the intervention group receive therapy with HR (one tablet of 500 mg twice daily for 8 weeks) in combination with regular treatment. Patients in the control group only receive regular treatment (consisting of ACT and ECT). No placebo medicine will be used in this study.

Use of co-intervention
Subject can use co-medication and other interventions if in accordance with usual care (e.g. stop antiplatelet drugs during ACT).

Escape medication
Subjects are allowed to use analgesics when experiencing pain of the affected leg in accordance with usual care (e.g. NSAID discouraged regarding bleeding risk).

Name and description of investigational product
The IMP for this study is HR, produced by GlaxoSmithKline under the tradename Venoruton®. It has market authorization and is registered as a medicine in the Netherlands. Its official indication is symptomatic treatment of CVI. Thus, our study utilizes a marketed IMP for a new indication.

Summary of findings from non-clinical studies
This is discussed in the Summary of Product Characteristics (SPC).

Summary of findings from clinical studies
This is discussed in the SPC.

Summary of known and potential risks and benefits

This is discussed in the SPC.

Description and justification of route of administration and dosage
In its medicinal form, HR is only available as a film-coated tablet of 500 mg administered by oral route. Its recommended dosage in CVI is 1000-1500 mg daily. [36] Its half-life varies between individual from 10 to 25 hours. [36]
We opted for twice daily ingestion of a 500 mg tablet. Since most patients will receive take their anticoagulant twice daily (hospital preference for Apixaban), twice instead of once daily ingestion of the IMP is not expected to influence treatment adherence.

Dosages, dosage modifications and method of administration
One film-coated tablet of Venoruton® is administered twice-daily by oral route. Dosage modifications are not applicable.

Preparation and labelling of Investigational Medicinal Product
The clinical pharmacy of Radboud University Medical Center prepares and labels the IMP in accordance with the Good Manufacturing Practice (GMP) guideline.

Drug accountability
Once prepared and labelled, the IMP is delivered and stored at the clinical pharmacy of the azM. Patients allocated to the intervention group will receive and start treatment with the IMP within 48 hours after diagnosis. The IMP is picked up at the clinical pharmacy by the researcher and delivered to the patient. Every patient receives 4 boxes of the IMP at once, each containing 30 tablets in medicine strips (2 daily x 7 days x 8 weeks = 112 required tablets). Upon treatment completion after 8 weeks, patients return these boxes upon their visit to the clinic. The researcher returns these boxes to the clinical pharmacy, where a pill count is performed to provide an estimate of compliance. Subsequently, the clinical pharmacy will destroy the remaining IMP.

Study burden and risks

Patients have a follow-up duration of 12 weeks after diagnosis of DVT. In addition to their visit at the ED, subjects will visit the outpatient clinic four times during follow-up. At each visit secondary outcomes are measured through standardized forms, anamnesis, blood drawing and assessment of the affected leg. Two visits (4 and 12 weeks) coincide with the regular clinical care pathway. The primary outcome, RVO, is measured at 12 weeks by echography and is also part of the regular care. Subjects allocated to the intervention group will take two oral tablets daily over a period of eight weeks. The IMP has been established as safe with rarely occurring, mild, reversible side-effects through many years of experience.

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

Adult; acute deep vein thrombosis; objectively confirmed deep vein thrombosis by duplex-echography; proximal deep vein thrombosis

Exclusion criteria

Previous deep vein thrombosis; bilateral deep vein thrombosis; pre-existent chronic venous insufficiency (CEAP >= C3); active malignancy; inflammatory disease; pregnancy; indication for therapeutic thrombolysis; contra-indication for a direct oral anticoagulant

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-12-2020
Enrollment:	44
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Venoruton
Generic name:	Hydroxyrutoside
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-05-2020
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-08-2020
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 26364
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-000749-15-NL
CCMO	NL73142.068.20
Other	NL8365
OMON	NL-OMON26364