Efficacy and safety of oral itraconazole in the reduction of epistaxis severity in hereditary hemorrhagic telangiectasia

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5.1 Study hypothesisThe primary study hypothesis states that oral treatment with itraconazole will reduce the epistaxis severity score (ESS) due to the anti-angiogenic effects of itraconazole.5.2 Research question and primary outcomeWhat is the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac and vascular disorders congenital
Study type	Interventional

Summary

ID

NL-OMON46365

Source
ToetsingOnline

Brief title
Itraconazole for epistaxis in HHT patients

Condition

- Cardiac and vascular disorders congenital
- Skin vascular abnormalities
- Vascular haemorrhagic disorders

Synonym
hereditary hemorrhagic telangiectasia, Rendu-Osler-Weber disease

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis

Source(s) of monetary or material Support: ZonMW Topzorg project; Stichting Wetenschappelijk Onderzoek Rendu Osler (SWORO)

Intervention

Keyword: Epistaxis, Hereditary hemorrhagic telangiectasia, Itraconazole, Rendu-Osler-Weber

Outcome measures

Primary outcome

The primary outcome of this study is the difference of epistaxis severity score

between the baseline and at the end of the trial.

Secondary outcome

Safety of itraconazole, side-effects, adverse events

Difference in monthly epistaxis severity measured with:

- Monthly number of episodes;

- Monthly duration;

- Monthly intensity;

- VAS score of epistaxis frequency, duration and intensity.

Difference in biochemical blood values: Hb and ferritin between baseline and

the end of the study.

Difference in quality of life with SF-36 between baseline and end of the study

Study description

Background summary

Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant inherited disease characterized by mucocutaneous telangiectasias and arteriovenous malformations (AVMs). The exact pathophysiology is still unclear, however elevated levels of vascular endothelial growth factor (VEGF) are believed to

play an important role in pathogenesis of HHT. The majority of HHT patients suffers from spontaneous recurrent epistaxis (nose bleeding) from the nasal telangiectasias. In addition, epistaxis in HHT patients can significantly decrease the quality of life. Treatment of epistaxis in HHT patients is difficult since standard measurements rarely have a sustained effect. In some cases, systemic therapies with either thalidomide or VEGF-inhibiting bevacizumab may be required to decrease epistaxis severity. However, neither of the systematic treatments are ideal for epistaxis treatment due to the severe side-effects of thalidomide and intravenous administration and high costs of bevacizumab. Recently it has been discovered that besides antifungal properties, itraconazole inhibits angiogenesis by inhibiting the VEGF-receptors. Itraconazole has already been used for its anti-angiogenic properties in human cancer studies and has shown great potential. Based on this evidence, the fact that VEGF is elevated in HHT patients and that VEGF inhibition has shown to reduce epistaxis, the antiangiogenic effects of itraconazole could potentially reduce epistaxis severity in HHT patients. In addition, itraconazole is an affordable, unpatented and generally well tolerated drug. Therefore itraconazole could potentially be a new, viable treatment option for severe epistaxis in HHT patients.

Study objective

5.1 Study hypothesis
The primary study hypothesis states that oral treatment with itraconazole will reduce the epistaxis severity score (ESS) due to the anti-angiogenic effects of itraconazole.

5.2 Research question and primary outcome
What is the effect of oral itraconazole treatment on the epistaxis severity score (ESS) in patients with moderate-severe epistaxis and hereditary hemorrhagic telangiectasia?

5.3 Secondary outcome(s)
- Safety of oral itraconazole in HHT patients with epistaxis. What the side-effects and (serious) adverse events?
- Difference in monthly epistaxis duration and frequency after treatment compared to baseline.
- Difference in the mean hemoglobin (Hb) and ferritin levels in HHT patients with epistaxis.
- Difference in quality of life in HHT patients with epistaxis following treatment.
- Effects of itraconazole on other HHT associated symptoms such as gastro-intestinal blood loss and presence of telangiectasias.

Study design

Open label, single-center, uncontrolled pilot-study

Intervention

daily 200 mg itraconazole for 16 weeks (4 months)

Study burden and risks

The burden consist of 4 extra visits, blood samples (5 times), recording a epistaxis diary and two times questionnaires (SF*36). There is a risk for the known side*effects of the itraconazole. The potential benefit for participating patients is that itraconazole may reduce the severity of epistaxis.

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 with HHT: Definite HHT according to the Curacao criteria (3 positive criteria or more) AND/OR genetically confirmed HHT
2. Suffering from epistaxis at least on average of 4 days per week;
3. In the last six months suffering from anemia or iron deficiency or in last twelve months use iron treatment or blood transfusions;
4. Failure or partial failure of local treatment with systemic treatment indicated by ENT specialist;
5. Adult (18 years or older at time of inclusion).

Exclusion criteria

1. Patients with any history of ventricular cardiac dysfunction;
2. Patients with elevated liver enzymes or any pre-existing liver disease or a history with known liver toxicity caused by medication;
3. Hypersensitivity or allergy for azole antifungal drugs;
4. Patients with a severe disease with a life-expectancy <1 year;
5. Women that are pregnant, nursing, have a pregnancy wish in the study period or who use anticonception inadequately;
6. Patients currently receiving chemotherapy;
7. Patients receiving drugscontraindicated when using itraconazole (see protocol chapter 14.1 section G of the study protocol for a full list)
8. Patients who do not understand English or Dutch language sufficiently enough;
9. Patients who refuse informed consent.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-08-2018
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sporanox
Generic name:	Itraconazole
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-01-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-05-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2017-003272-31-NL
CCMO	NL62902.100.17