An uncontrolled, open label pilot-study assessing the efficacy in reducing bleeding severity, and the safety of oral tacrolimus in patients with hereditary hemorrhagic telangiectasia

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Study hypothesisThe primary study hypothesis states that oral treatment with tacrolimus will reduce the bleeding severity in HHT.Research question and primary outcomeWhat is the effect of oral tacrolimus treatment on hemoglobin levels in HHT...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular haemorrhagic disorders
Study type	Interventional

Summary

ID

NL-OMON48255

Source
ToetsingOnline

Brief title
Tacrolimus for bleeding in HHT patients

Condition

- Vascular haemorrhagic disorders

Synonym
hereditary hemorrhagic telangiectasia, Rendu-Osler-Weber syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W,Het Kees Westermann Fonds (Stichting Wetenschappelijk Onderzoek Rendu Osler (SWORO))

Intervention

Keyword: Epistaxis and gastrointestinal bleeding, Hereditary hemorrhagic telangiectasia, Rendu-Osler-Weber syndrome, Tacrolimus

Outcome measures

Primary outcome

The primary study outcome is the difference in hemoglobin level at baseline

compared to the level of hemoglobin after 20 weeks of treatment

Secondary outcome

The ESS

The ESS is a score of the epistaxis severity, specifically designed for HHT

patients [Hoag et al., 2010]. The ESS consists of six questions concerning

epistaxis severity within the last six months with regards to 1) frequency, 2)

duration, 3) intensity of bleeding, 4) if patients have sought medical

attention, 5) if patients are anemic and 6) if patients received a blood

transfusion. The ESS is frequently used in HHT research and also used to

measure efficacy of treatment.

Epistaxis diary

In the St. Antonius Hospital an epistaxis diary (*Dagboek bloedneuzen*)

concerning daily epistaxis number, severity and duration is currently being

used in the clinical practice of HHT treatment to measure epistaxis severity.

This will be used to estimate the frequency, duration and severity of epistaxis in this trial.

Visual Analogue Scale (VAS)-score

A VAS-score ranging from 0 (no complaints) to 10 (very severe complaints) concerning epistaxis severity and influence of epistaxis on social life will be filled in by the patients.

QoL * SF-36

The Quality of Life (QoL) will be assed with the short form 36 (SF-36). This is a questionnaire with 36 that measures patient-reported survey of patient health. The questionnaire will be used at inclusion (BV) and at the end of the study (T20)

Fatigue * MFI-20

The fatigue complaints of the patients will be assessed with Multidimensional fatigue inventory. This is a questionnaire designed to measure the patient*s fatigue and consists of 20 questions. The questionnaire will be used at inclusion (BV) and at the end of the study (T20)

Blood panel values

Every visit blood panel values will be evaluated including a complete blood count (Hb, hematocrit (Ht), , leukocytes, thrombocytes) iron status (ferritin, transferrin, transferrin saturation), liver function (aspartate transaminase

(ASAT), alanine transaminase (ALAT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin and albumin), kidney function (urea, creatinine), C-reactive protein (CRP), glucose, and blood electrolytes (sodium and potassium). In addition, level of tacrolimus will be measured. Furthermore, at the baseline visit and during the therapy soluble VEGF-receptor 1 (sVEGFR-1) / soluble fms-like tyrosine kinase-1 (sFlt-1) and pentraxin 3 (PTX 3) will be determined. Both PTX3 and sFlt-1 are possible predictors for epistaxis severity. PTX 3 will be analyzed in this hospital. The sFLT-1 will be analyzed in Leiden University Medical Center.

Study description

Background summary

Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant inherited disease, characterized by multisystemic abnormal vasculature [Govani and Shovlin, 2009]. The prevalence of HHT is approximately 1 in 8000 individuals with regional differences according to geographic location [Guttmacher et al., 1995; Dakeishi et al., 2002; Westermann et al., 2003]. Clinical features of HHT consist of the presence of recurrent spontaneous epistaxis (nosebleeds), mucocutaneous telangiectasias and visceral arteriovenous malformations (AVMs) usually located in the lungs, liver and brain. The quality of life of HHT patients is frequently severely affected by the severe epistaxis [Geirdal et al., 2014; Geisthoff et al., 2012; Zarabeitia et al., 2017]. The treatment of epistaxis in HHT patients is challenging because standard epistaxis management such as cautery rarely has a durable effect [Shah et al., 2002]. In cases of severe epistaxis, invasive surgical measures such as laser photocoagulation, septodermoplasty and complete nostril closure (Young*s procedure) and systemic medical treatment are used in an attempt to reduce epistaxis severity [Garg et al., 2014; Chin et al., 2016]. Endoscopic treatment with argon plasma coagulation (APC) has demonstrated to reduce transfusion needs in HHT patients with severe gastrointestinal bleeding, although the results may be less satisfactory as in the non-HHT population [Sargeant et al., 1993]. Apart from endoscopic treatment options, several medical treatments have been postulated including hormonal therapy, antifibrinolytics, and thalidomide [Faughnan et al., 2011]. Unfortunately, to date, none are recommended in the current HHT

guidelines due to lack of evidence [Faughnan et al., 2011]. Bleeding in HHT is a chronic problem that requires continuous monitoring and treatment. Even with treatment, severe epistaxis and/or gastrointestinal bleeding may result in iron-deficient anemia which sometimes requires intravenous iron treatment or blood transfusions.
HHT is caused by disruption of the transforming growth factor (TGF) * signaling pathway due to mutations in the genes encoding for Endoglin (ENG, chromosome 9q34), activin A receptor type II-like 1 (ACVRL1/ALK1, chromosome 12q13) or Mothers against decapentaplegic homolog 4 (SMAD4, chromosome 18q21) which cause HHT type I (OMIM #187300), HHT type II (OMIM #600376), and the combined Juvenile Polyposis/HHT syndrome (OMIM #175050), respectively [McAllister et al., 1994; Johnson et al., 1996; Gallione et al., 2004]. These genes in the TGF * pathway are highly expressed in vascular endothelial cells and play an important role in angiogenesis and vascular function. Haploinsufficiency in ENG and ACVRL1 is recognized at the underlying cause of HHT [Ardelean and Letarte, 2015]. In addition, evidence exists that elevated levels of vascular endothelial growth factor (VEGF) also interplay in the pathological mechanism of the HHT phenotype. This is supported by the fact that increased plasma levels of VEGF have been found in HHT patients [Cirulli et al., 2003; Sadick et al., 2005].
Tacrolimus, an immunosuppressive drug, used for prevention of organ transplant rejection, has recently been investigated as therapeutic option for HHT. In Vitro, tacrolimus has shown to increase ALK1 and ENG signaling [Albinana et al., 2011; Ruiz et al., 2017]. Moreover, tacrolimus has shown to inhibit angiogenesis by anti-VEGF effects [Ardelean and Letarte, 2015; Ruiz et al., 2017]. In a case-report with a patient suffering from HHT and pulmonary arterial hypertension, tacrolimus treatment reduced the epistaxis significantly and decreased fatigue symptoms [Sommer et al., 2019]. In the Netherlands, 3 HHT patients are currently being treated with tacrolimus as last resort option (of which 2 in our HHT center). An adult female, received tacrolimus for her high-output heart failure caused by her liver AVMs, another adult female for severe epistaxis and a child suffering from melena due to severe gastrointestional telangiectasia requiring blood transfusions have been treated. The complaints in all three cases have significantly reduced in severity. The target value of tacrolimus for HHT (between 2-3 ng/L) is lower compared to use in organ transplant recipients (for example lung transplant recipients: 5-15 ng/L). In current HHT research, tacrolimus has gained a lot of interest and the first trial with nasal tacrolimus ointment for severe epistaxis has recently been completed (NCT03152019) with fairly good results as presented on the international HHT conference 2019. The lack of good alternatives for severe bleeding treatment, and current data concerning HHT and tacrolimus treatment are reason enough to investigate this treatment further. In addition, the expected side-effects of tacrolimus are much less because much lower serum levels of tacrolimus have shown significantly positive effects on epistaxis than are needed for organ transplant recipients. Therefore, we designed a non-randomized, open label, pilot-study to investigate the effects of oral tacrolimus on bleeding severity in HHT patients.

Severe bleeding in HHT is a chronic problem that requires continuous monitoring and treatment. For severe cases, with daily epistaxis or iron infusion and red blood cell transfusion dependent patients, systemic treatment with thalidomide or bevacizumab are the last resort options to treat the severe anemia [Dupuis-Girod et al., 2012; Invernizzi et al., 2015]. However, these options are not ideal. The severe side-effects of thalidomide such as severe drowsiness and peripheral polyneuropathy are reason enough to stop therapy. A study performed in the St. Antonius Hospital showed that only a minority of the HHT patients continued taking thalidomide due to severe side-effects despite strong reduction in epistaxis severity [Hosman et al., 2015]. Bevacizumab has been demonstrated to be effective, however the intravenous administration and high costs make the drug as first choice less attractive [Bose et al., 2009; Dupuis-Girod et al., 2012]. So, the warrant for new, affordable and safe drugs is still present for the treatment of severe bleeding in HHT. Tacrolimus has shown promising results in vitro and in vivo. Tacrolimus could therefore potentially be a good alternative for thalidomide and bevacizumab in the treatment of epistaxis and/or gastrointestinal bleeding in HHT patients.

Study objective

Study hypothesis
The primary study hypothesis states that oral treatment with tacrolimus will reduce the bleeding severity in HHT.

Research question and primary outcome
What is the effect of oral tacrolimus treatment on hemoglobin levels in HHT patients with severe bleeding from epistaxis and/or gastrointestinal bleeding with the need for iron treatment and/or blood transfusions despite extensive local treatment?

Secondary outcome(s)
* The epistaxis severity score (ESS)
* Frequency and severity of epistaxis measured with epistaxis diary in HHT
* 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 tacrolimus on other HHT associated symptoms such as gastrointestinal blood loss and presence of telangiectases.
* Safety, side-effects and (serious) adverse events of oral tacrolimus in HHT patients with epistaxis.
* Long term efficacy at 1 and 3 months after tacrolimus treatment on severity of epistaxis.

Study design

General description
An open label, single-center, uncontrolled pilot-study with 20 HHT patients with severe bleeding will be performed. Patients will receive standard care for epistaxis and/or gastrointestinal bleeding and once daily tacrolimus (Advagraf® met gereguleerde afgifte (MGA)) for 20 weeks.

Duration of the trial
The duration of the trial will be 24 weeks. The first four weeks patients will record their epistaxis severity in a diary, followed by 20 weeks treatment. Following the trial, tacrolimus will be stopped and patients will be followed up by the researcher to investigate the long-term efficacy at 1 and 3 months. If bleeding will reoccur, patients are allowed to restart tacrolimus treatment and the patients will be monitored by the treating pulmonologists as well of the St. Antonius Hospital.

Participating center(s)
St. Antonius Hospital, Nieuwegein, department of pulmonology, cardiology, gastroenterology and department of Ear, Nose, and Throat (ENT).

Study timeline
* Study start: November 2019.
* Recruitment end: March 2020.
* Study end: June 2020.
* Completion of Clinical Study Report (CSR): July 2020.
* Publication date: November 2020.

Intervention

Patients will receive once daily oral tacrolimus (Advagraf® MGA) for 20 weeks with a target value of 2-3 *g/L tacrolimus. The initial dose will be 1 mg daily of tacrolimus. The dose of tacrolimus will be increased or decreased based on the target value (with steps of 0.5 * 1 mg per week). The estimated required dose needed to acquire the tacrolimus target value of 2-3 *g/L is 3-5 mg per day. The target value is based on a case-report with tacrolimus and HHT, and 3 patients currently being treated with tacrolimus for HHT related symptoms [Sommer et al., 2019].

Study burden and risks

The burden consist of 4 extra visits, several blood samples, recording an epistaxis diary and filling in questionnaires (SF*36 and MFI-20). There is a risk for the known side*effects of the tacrolimus, although much lower than reported in the literature due to lower target value required for beneficial effects on HHT symptoms. The potential benefit for participating patients is

that tacrolimus may reduce the severity of bleeding.

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

* Patients with HHT:
o Definite HHT according to the Curacao criteria (3 positive criteria or more)
AND/OR
o Genetically confirmed HHT
* Suffering from epistaxis at least on average of 4 days per week or documented gastrointestinal teleangiectasis by endoscopy with suspicion of bleeding;
* In the last six months suffering from anemia, iron deficiency or use iron treatment or blood transfusions;
* Failure or partial failure of local treatment with systemic treatment

indicated by ENT specialist or gastroenterologist;
* Adult (18 years or older at time of inclusion).

Exclusion criteria

* Hypersensitivity or allergy for tacrolimus
* Patients with a severe disease with a life-expectancy <1 year;
* Women that are pregnant, nursing, have a pregnancy wish in the study period or who use anticonception inadequately;
* Patients currently receiving chemotherapy;
* Severe kidney disease
* History of severe ventricular cardiac dysfunction
* A negative advise of a clinical pharmacist in cases with concurrent use of drugs that have a clinically relevant interaction with tacrolimus.
* Patients who do not understand English or Dutch language sufficiently enough;
* 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):	12-03-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Advagraf

Generic name:	Tacrolimus
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-09-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-12-2019
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	EUCTR2019-003585-40-NL
CCMO	NL71405.100.19