Treatment of congenital vascular malformations using Sirolimus: improving quality of Life

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Vascular disorders NEC
Study type	Interventional

Summary

ID

NL-OMON45838

Source
ToetsingOnline

Brief title
Treatment of congenital vascular malformations with Sirolimus

Condition

- Vascular disorders NEC

Synonym
congenital vascular malformations ; vascular anomalies

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMw,Pfizer

Intervention

Keyword: mTor inhibitor, quality of Life, Sirolimus, vascular malformation

Outcome measures

Primary outcome

To investigate whether Sirolimus results in a significant and clinically

relevant reduction of pain and an

improved quality of life in patients with untreatable vascular malformations.

Secondary outcome

What length of therapy is required to have and maintain adequate pain reduction?

Will response to Sirolimus prolong after stop treatment or will there be a

rebound?

Will Sirolimus only have effect on pain reduction or will Sirolimus also

inhibit growth/progression of the

vascular malformation or even lead to reduction of the size of the vascular

malformation?

Which long term consequences can be observed after treatment with Sirolimus

e.g. in children?

Are there genetic factors in the vascular malformation that can predict outcome

of treatment with Sirolimus?

Will Sirolimus lead to a more cost-effective treatment for this patient group?

Study description

Background summary

Congenital vascular anomalies are uncommon and belong to the group of rare diseases. In 1996, the International Society of the Study of Vascular Anomalies adopted a new classification, distinguishing vascular malformations from vascular tumors. This classification was revised in 2014 and newly identified genetic features were taken into account. Vascular malformations feature dysplastic malformed vessels and are a consequence of a defective development of the embryonic vascular system. Vascular malformations can involve lymphatic vessels, capillaries, veins and arteries or even combinations. These vascular malformations are present at birth and grow with the child. Treatment options range from conservative to
surgical extirpation or intralesional embolisation/sclerosis . Unfortunately, this is often not enough. Many patients still have complaints like severe pain and invalidation due to the lymphatic or venous malformation making a normal functional life impossible. These vascular malformations can cause serious complications including obstruction of vital organs and their function, recurrent infection and significantly reduced quality of
life of persons affected. As the natural course of the disease affects multiple body systems, the therapeutic management is challenging. To date, no other medical treatment options are available. Although standard pain medication is given according the (inter) national pain protocols, patients still suffer pain and are not able to function normally in daily life. Majority (60-70% percent of the patients) of the patients is not able to
have a normal life, with a normal job and normal social activities. Children are often not able to go to school normally, cannot play outside and have pain at the site of the malformation. The vast majority of literature reporting medical therapies for vascular anomalies consists of case reports and small series and is complicated by publication bias (negative findings are often not published), inconsistent use of nomenclature, and the absence of clinical trials. Recent case reports mention the positive effects of refractory patients with Sirolimus. Sirolimus, also known as rapamycin, is currently the only FDA-approved mTOR inhibitor, indicated for prevention of kidney allograft rejection in adults and children 13 years or older,
but is commonly used to manage organ rejection in younger children. mTOR is a serine/threonine kinase that is regulated in the cell by
phosphoinositiede-3-kinase (PI3K) and Akt.In patients with vascular malformations mutations in the mTOR pathway occur leading to increased activation of mTOR. For example, in patients with venous malformations mutations in the gene encoding for TIE2 (=endothelial cell tyrosine kinase receptor 2) occur in almost 50% of cases leading to a chronic activation of AKT. In patients with lymphatic malformations similar mutations can be found leading to the same activated pathway. Inhibition of this pathway in patients with vascular malformations seems therefore very rational.
In the literature more than 85 cases of all kind vascular malformations have been published so far. All showing a positive effect of Sirolimus in the treatment of vascular malformations. Based on all these case reports it seems Sirolimus is a panacea, however, we believe this is most probably caused by a publication bias i.e. we think that failures of treatment are not reported.

Although the number of patients treated in our hospital center is still small (n=8), one patient did not respond to Sirolimus treatment underlining this hypothesis. For this reason we want to perform an open label study with Sirolimus in patients that have congenital vascular malformations that cannot be treated by other conventional techniques.

Study objective

As patients with congenital vascular malformations often suffer from severe pain and morbidity due to the vascular malformation, quality of life is often signifcantly impaired. The primairy objective of the present study is to reduce pain complaints and in this way improving the quality of life of the patients.

Study design

The diagnosis of vascular anomaly has been made previously based on clinical, radiographic and//or histological criteria. mTOR inhibitors, such as Sirolimus, have been postulated to be beneficial in the treatment of these complex vascular anomalies were no other conventional treatment options are present. Sirolimus is currently the only FDA and EMA-approved mTOR inhibitor. To make sure that only patients that have no other treatment options will be included, a independent committee will evaluate the patient whether he/she is eligible for the present study. All patients will be treated for six months with Sirolimus, followed by at time period without treatment . If pain complaints return a second phase of one year with treatment of Sirolimus will start (rechallenge).
As control, the chronic history as has been documented in the medical records of the patients will be used. Before start of the study the chronic history of the patients will be documented and data will be entered in a GCP certified data-management system (Castor) that is already operational. In addition, for start of the study all patients will have an assessment regarding quality of life and a recent MRI of the vascular malformation. Furthermore, patients will be asked to keep a diary in two months before start with Sirolimus to monitor complaints of pain (using the VAS score). The quality of life assessments are being performed to gain insight in the burden of the disease in daily life and the influence of pain experienced by patients in daily life. After six months of treatment the possible effect of Sirolimus on the vascular malformation is being evaluated by MRI. In addition, Quality of Life assessments will be performed again at, six and at the end of the study (12 months). Total duration of inclusion of patients in the study will be 2.5 years. All patients will have at least one year follow up after the six months treatment meaning that the end of study will be after 4.0 years. The study will be performed according the GCP guidelines.
All patients will be included and start the trial in Nijmegen, as regular controls will take place also in Nijmegen . Sirolimus has been provided for all patients, however, is only send and stored at the Radboudumc. However, if

necessary, controls in between for example in case of fever, will be done as close as possible to the place where patients live.

Intervention

The intervention is treatment with Sirolimus

Study burden and risks

The agent Sirolimus is extensively known from the treatment of patients with kidney transplants. For this reason the side effects of Sirolimus are well known, although Sirolimus in renal transplant patients is always given in combination with other agents such as cyclosporine and corticosteroids. As these drugs are converted through the same pharmacological pathway you can expect this to affect the risk of side effects. Given the fact that patients with vascular malformations will receive Sirolimus as a single agent (if any pain medication except acetaminophen is stopped prior study in order to adequately assess the effect of sirolimus on the pain), it is expected that the risk of side effects is much lower. In the 12 patients who have been treated at our center , 1/3 of patients developed after start of Sirolimus aphthous lesions in the mouth that mostly disappeared within 2 weeks, one patient had passagere hepatic impairment, one patient had had a passagere hypertriglyceremie and one patient developed hypophosphatemia when Sirolimus levels were higher. After lowering the Sirolimus is this side effect disapeared. In our view, all side effects associated with a low risk profile.
The burden that exist for the patients, in particular for those that have to travel for a larger distance, are the regular visits that have to take place in Nijmegen, including blood withdrawal each time that they have a control appointment. Although this burden is present, especially for those patients who come from further, there is no increased risk associated with them and the burden is in our opinion minimal. Furthermore, the patient will have at start of the study as well as after six months a MRI of the vascular malformation. All children participating in the study will be adequately accompanied pedagogical staff to minimize the burden of having MRI.
Finally, questionnaires are completed with respect to quality of life for both children and parents and for the adult participants. The burden of this is mainly the time it costs. Some of the patients are already known to the medical psychologist and have already completed the questionnaires. Depending on how long ago this have been done, these questionnaires will be filled again.

In conclusion, the estimate of the risk and burden of the present study is in our opinion acceptable with minimal risk (e.g. possible side effects of Sirolimus)

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

• Diagnosis of Congenital venous malformation, or lymphatic malformation or combined.
• Age between 1-70 years.
• Patients (or legal guardians for children) have to be able to sign the informed consent
• Patients are either refractory to standard care such as medical treatment (low molecular weight heparines, pain medication etc.), surgical resection and/or sclerotherapy/embolization (ineffective or accompanied by major complications) or there is no possibility for surgical intervention anymore. Only patients that have a normal clinical screening (no signs for infection, normal bone marrow function, normal liver and kidney function, normal glucose metabolism etc.) can be included.

• Patients included have no cardiac impairment
• Patients have no gastrointestinal impairment as Sirolimus is absorbed gastro-intestinal and normal function is needed
• No other underlying medical disorder like Down syndrome or other syndromes
• Women of reproductive age have to be informed that contraceptive methods are mandatory during the study time, pregnant women are excluded as also breast-feeding women
• Karnofsky score > 50

Exclusion criteria

• No written informed consent
• Known hypersensitivity to drugs or metabolites from similar classes as study treatment
• Patient has other concurrent severe and /or uncontrolled medical condition that would, in the investigator*s judgment, contraindicated participation in the clinical study (e.g. acute or chronic pancreatitis, liver cirrhosis, active chronic hepatitis, severely impaired lung function with a spirometry <= 50% of the normal predicted value and/or O2 saturation <= 88% at rest, etc.)
• Recent history of primary malignancy <= 5 years
• Impaired cardiac function or clinically significant cardiac diseases
• Immunocompromised patients, including known seropositivity for HIV
• Patient with any other concurrent severe and /or uncontrolled medical condition that would,in the investigator*s judgment, contraindicated participation in the clinical study.
• Pregnant or lactating women
• Karnofsky score < 50

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-09-2017
Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sirolimus
Generic name:	Rapamycin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-07-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-09-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2016-002157-38-NL
CCMO	NL57911.091.17