Efficacy of RAD001/everolimus in Autism and NeuroPsychological deficits in children with TSC (RAPIT-trial)

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The objective of this study is to determine whether influencing the protein pathway thought to underlie TSC by Everolimus treatment will improve cognitive abilities in these children.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON39487

Source
ToetsingOnline

Brief title
RAPIT-trial

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Bourneville's disease, Tuberous sclerosis complex (TSC)

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Sophia Stichting Wetenschappelijk Onderzoek (SSWO) en Hersenstichting

Intervention

Keyword: Autism, Neuropsychological deficits, RAD001/Everolimus, Tuberous Sclerosis Complex

Outcome measures

Primary outcome

To determine the effect of Everolimus on cognitive development (measured by IQ) in children with TSC.

Secondary outcome

To evaluate the effect on symptoms of autism spectrum disorder, other (neuro) psychological test parameters, seizure frequency, EEG-abnormalities and specific symptoms of learning disability. Furthermore, we will observe the tolerability of Everolimus in children with TSC.

The MRI will show structural abnormalities in the brains of the participants. We can evaluate the size of these abnormalities before and after Everolimus treatment, and relate these abnormalities to the cognitive abilities of that participant. Moreover, we want to investigate whether improvement of the structural abnormalities in the brain is accompanied by an improvement of the cognitive abilities of that participant.

Study description

Background summary

Tuberous sclerosis complex (TSC) is a genetic disorder with an approximate birth incidence of 1:6.000-10.000. The brain shows typical cortical and subcortical malformations, called tubers, giving the disease its name. The majority of children with TSC show epilepsy (90%), many with mental retardation (IQ <80), autism, behavioral problems and/or learning disabilities. These

symptoms have a negative impact on quality of life of patients and their families.
Preclinical studies from our lab and other labs showed that the TSC mouse model is a good model for the disease. For instance, TSC mutants show epilepsy, learning deficits, and social behavior deficits. Preclinical studies using mouse models further revealed that the TSC pathway plays a critical role in the protein synthesis dependent phase of synaptic plasticity. Loss of TSC gene function causes increased activity of mTOR, and results in synaptic plasticity deficits.
Importantly, recent pre-clinical studies also showed that epilepsy, as well as deficits in plasticity and cognition, can be ameliorated by early treatment with Everolimus, a specific and potent inhibitor of mTOR. Clinical trials in adult TSC patients suggest that Everolimus can rescue some of the symptoms of TSC patients, such as renal tumors (angiomyolipoma) and brain tumors (subependymal giant cell astrocytoma). Moreover, a case study showed a dramatic improvement of epilepsy in a child with TSC treated with Everolimus. Together these findings suggest that early treatment with Everolimus may reduce the development of the neurological problems associated with TSC.
TSC is a rare disease, but due to its consequences, affects patients and families severely. It is a unique syndrome with respect that the underlying deficit in protein function can be partly rescued by a drug that is already registered for use in humans. This drug is highly specific. In mouse models administration of this drug improves seizures and learning. This suggests that there is a good chance that the symptoms of children with TSC will improve with this medication.

Study objective

The objective of this study is to determine whether influencing the protein pathway thought to underlie TSC by Everolimus treatment will improve cognitive abilities in these children.

Study design

After informed consent, participants will be randomized to Everolimus or placebo treatment for 12 months. This study is doubleblind.

Intervention

Treatment with Everolimus or placebo.

Study burden and risks

TSC patients with a (severe) deficit on cognitive, social and motor level are often not able to take care of themselves. Most of these patients have to be looked after day and night, and some of them are institutionalized. For these

patients, further development of their cognitive, social and motor skills would mean they can communicate (more) with other people, that they understand the world around them and they might even become able to take care of themselves. Everolimus has side effects, but the medication these patients take on a daily basis to control the several features of TSC have similar side effects.

The study burden for participants will be
- taking the medication
- possible side effects. We will try to minimize the side effects by lowering the dose when side effects occur. All side effects are dose dependent. Frequently observed side effects include diarrhea, mouth ulcers and skin rash. Rare side effects are headache, peripheral edema, infectious diseases and slowed wound healing. Parents will receive detailed information about when to contact a doctor. The side effects caused by Everolimus are similar to those of the other medication these patients use. No fatal side effects were reported in TSc patients.
- Two EEGs (an additional one or two times compared to standard treatment)
- Two neuropsychological examinations
- Eight times a capillary bloodtest (vingerstick) for determining bloodlevels. In regular care TSC children have bloodtests at least once a year.
- Twice MRI (1 or 2 additional MRIs compared to regular follow-up
- Possible anaesthesia during MRI, with a chance of allergic reaction to the anaesthetic.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Children with a definite diagnosis of TSC between 4 and 17 years.
Estimated IQ <80 and/or special schooling and/or autism spectrum disorder and/or learning disability requiring remedial teaching.
Written informed consent by parents/care-takers, and the patient if he or she is 12 years or older and cognitively able to consent.

Exclusion criteria

Hepatic dysfunction.
Surgery less than 6 weeks before entering the study.
Infection at time of inclusion.
Allergy for any of the components of the study medication.
Additional diseases or disorders that may influence the endpoints.
Developmental age estimated below 3.5 years.
Intractable epilepsy with more than 1 seizure per week.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-11-2012
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Votubia
Generic name:	Everolimus
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	02-12-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-03-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2012
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2010-019519-39-NL
CCMO	NL38619.078.11