Sirolimus (Rapamune®) for the treatment of anti-Hu associated paraneoplastic neurological syndromes

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

Summary

ID

NL-OMON32182

Source
ToetsingOnline

Brief title
Sirolimus in PNS

Condition

- Autoimmune disorders
- Central nervous system infections and inflammations

Synonym
Paraneoplasia, remote effect of cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Gratama Stichting

Intervention

Keyword: Anti-Hu antibodies, Paraneoplastic neurological syndrome, Sirolimus, Small cell lung cancer

Outcome measures

Primary outcome

The primary endpoint of the study is the functional and neurological improvement after 8 wees of sirolimus. Functional improvement is defined as a decrease of one point or more on the Rankin scale after the 8th week of sirolimus as compared to the baseline evaluation. Improvement of neurological impairment is defined as a positive score (>0) in the EFIT overall evaluation after the 8th week of sirolimus as compared to the baseline evaluation.

Secondary outcome

The secondary research variables are anti-Hu antibody titers in serum and CSF, antigen specific T cells in blood and CSF, oculomotor function, sirolimus concentration in serum and CSF and MDR1 polymorphisms and improvement in the Barthel Index, AMC Linear Disability Score and the PNS Neurological scale.

Study description

Background summary

Paraneoplastic neurological syndromes (PNS) are devastating neurological syndromes that are not directly caused by the tumor or its metastases nor by vascular, metabolic, infectious or treatment related causes. The detection of antineuronal auto-antibodies directed against antigens that are expressed in the underlying tumor and in the nervous system has let to the autoimmune hypothesis of PNS and has facilitated diagnosis of PNS. The most common paraneoplastic antibody is directed against the Hu-antigens (anti-Hu). Hu-PNS is probably caused by an auto-immune reaction directed at the Hu-antigens in the tumor that subsequently reacts with the same or similar antigens in the

nervous system. Recent studies indicate that T-cells are a major cause of the neuronal damage. Sirolimus is a powerful inhibitor of activated T-cells. Therefore, this study investigates the hypothesis that sirolimus can effectively treat Hu-PNS by inhibiting activated T-cells.

Study objective

The primary objective of the trial is to study the efficacccy of sirolimus in paraneoplastisch neurological syndromes associated with anti-Hu antibodies (Hu-PNS)
Secondary objectives are to correlate clinical improvement with anti-Hu antibody titers in serum and cerebrospinal fluid (CSF), HuD specific T cells in blood and CSF, sirolimus levels in blood and CSF and with MDR1 polymorphisms.

Study design

Prospective, open-label, single center, phase II, 'prove of concept' study

Intervention

Treatment will be initiated with an oral loading dose of 6 mg sirolimus per day for three consecutive days followed by oral maintenance dosing of 3 mg/day. The dosing will be adjusted weekly to maintain through concentrations of 8-12 ng/ml.

Study burden and risks

The prognosis of paraneoplastic neurological syndromes associated with anti-Hu antibodies (Hu-PNS) is dismal. At present no treatment is available. The side effects of sirolimus can be relatively easily managed when weekly levels are determined. In addition, patients are treated for only 8 weeks with sirolimus in this study. Moreover, we do not expect adverse effects of sirolimus on tumor growth; on the contrary, an oncolytic effect is more likely.

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

i) PEM/PSN associated with high (>=1:400 by IIF) titer anti-Hu antibodies.
ii) IIF (indirect immunofluorescence) has been confirmed by Western blotting using purified HuD fusion protein as substrate.
iii) The neurological symptoms must still be progressing defined as neurological deterioration over the last 4 weeks.
iv) Patients aged >=18 years.
v) Patients who receive or will receive concomitant anti-tumor therapy are allowed to participate.
vi) Patients who have given written informed consent.

Exclusion criteria

i) Patients who have reached a neurological plateau phase more than 4 weeks before inclusion date (*damage is done*).
ii) Patients who are unwilling to undergo lumbar puncture.
iii) Liver enzyme elevations of more than 5-fold normal values
iv) Renal failure (GFR < 30 ml/min)
v) Extreme hypertriglyceridemia (> 10 mmol/L) and extreme hypercholesterolemia (> 10 mmol/L)
vi) Active infection
vii) Women of childbearing potential who are pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions.

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):	01-09-2008
Enrollment:	17
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	27-02-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	05-05-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	06-06-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-07-2012
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	EUCTR2008-000793-20-NL
CCMO	NL21957.078.08