Tysabri in PNS

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON28171

Source
Nationaal Trial Register

Brief title
na

Health condition

paraneoplastic neurological syndromes
paraneoplastic encephalomyelitis
paraneoplastic limbic encephalitis
Paraneoplastic cerebellar degeneration
Paraneoplastic sensory neuronopathy
anti-Hu antibodies
small cell lung cancer
natalizumab

Sponsors and support

Primary sponsor: Erasmus MC, Rotterdam
Source(s) of monetary or material Support: Verrichter = sponsor
Subsidie van Biogen Nederland

Intervention

Outcome measures

Primary outcome

Functional improvement with one point or more on the modified Rankin scale after the 12th week of natalizumab (compared to baseline).

Secondary outcome

Neurological improvement and safety. Neurological improvement is defined as a positive score (>0) in the EFIT overall evaluation and improvement on the AMC linear disability scale, Barthel index and PNS neurological scale after three natalizumab infusions (the 12th week of natalizumab), compared to baseline. Safety is assessed by CTC AE 4.0 criteria, from date of registration until 28 days after last study drug administration.

Study description

Background summary

Rationale: Paraneoplastic neurological syndromes (PNS) are ‘remote effects’ of cancer. It is thought that expression of Hu antigens by the tumor provokes an autoimmune response not only directed against the tumor but also against nervous tissues. PNS disorders are rapidly progressive over weeks to months leaving the patient severely debilitated. At the time of neurological presentation, 70% is not yet known with cancer which often makes the diagnosis difficult 1-4. The most frequent PNS is associated with anti-Hu autoantibodies (Hu-PNS). Hu-PNS is a monophasic, severe, Th1 mediated organ specific autoimmune disease.5, 6 Plasma exchange, corticosteroids, cyclophosphamide and intravenous immunoglobulins (IVIG) are generally considered not effective in the treatment of Hu-PNS and immunosuppressive or immunomodulating treatment is at present not recommended.9 Other than anti-tumor therapy after the detection of the tumor, no effective treatment for Hu-PNS is available. Functional improvement rarely occurs (<10%) and most of the patients ultimately die from the severe neurological disorder and not from the underlying malignancy.1, 2, 4 Better treatment modalities for PNS are a highly unmet medical need. Natalizumab may contribute to reduced activation of T cells already present in the CNS, leading to apoptosis and strongly inhibits migration of activated T cells to the CNS and consequently lowers damage done to the CNS by these cells during Hu-PNS.

Objectives:
Primary Objective: functional improvement with one point or more on the modified Rankin scale after the 12th week of natalizumab (compared to baseline).

Secondary Objectives: neurological improvement and safety. Neurological improvement is defined as a positive score (>0) in the EFIT overall evaluation and improvement on the AMC linear disability scale, Barthel index and PNS neurological scale after three natalizumab infusions (the 12th week of natalizumab), compared to baseline. Safety is assessed by CTC AE 4.0 criteria, from date of registration until 28 days after last study drug administration.

Study design: This is an uncontrolled single center phase II study testing 3 monthly infusions of natalizumab in 20 patients.

Study population: 20 patients with Hu-PNS; expected median age 60-65 years.

Intervention: Natalizumab 300 mg, intravenous infusions q 4 weeks for a maximum of 3 infusions over 12 weeks.
Main study endpoint: The primary endpoint is the functional improvement with one point or more on the modified Rankin scale after the 12th week of natalizumab (compared to baseline).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The direct side effects of the 3 (maximum) natalizumab infusions are mild and manageable. Potential serious side effects include PML and induction of tumor growth. However, the risk of these serious side effects is considered very low, as discussed in sections 1.2.6 and 13.1 of the protocol. The main burden for the patients are a short admission (1-2 nights); 3 natalizumab infusions (1 during admission; 2 in daycare); 2 additional outpatient visits, all at Erasmus MC department of Neurology. In addition, 2 lumbar punctures and 4 venapunctures are performed. During all 5 (maximum) visits, general physical and neurological examinations will be performed; 2 questionnaires (Barthel and AMC linear disability scale), nine hole peg test, ten metre walking test, Williams delayed recall test and Boston aphasia severity scale will be taken.

Study objective

Paraneoplastic neurological syndromes (PNS) are ‘remote effects’ of cancer. It is thought that expression of Hu antigens by the tumor provokes an autoimmune response not only directed against the tumor but also against nervous tissues. PNS disorders are rapidly progressive over weeks to months leaving the patient severely debilitated. At the time of neurological presentation, 70% is not yet known with cancer which often makes the diagnosis difficult 1-4. The most frequent PNS is associated with anti-Hu autoantibodies (Hu-PNS). Hu-PNS is a monophasic, severe, Th1 mediated organ specific autoimmune disease.5, 6 Plasma exchange, corticosteroids, cyclophosphamide and intravenous immunoglobulins (IVIG) are generally considered not effective in the treatment of Hu-PNS and immunosuppressive or immunomodulating treatment is at present not recommended.9 Other than anti-tumor therapy after the detection of the tumor, no effective treatment for Hu-PNS is available. Functional improvement rarely occurs (<10%) and most of the patients ultimately die from the severe neurological disorder and not from the underlying malignancy.1, 2, 4 Better treatment modalities for PNS are a highly unmet medical need. Natalizumab may contribute to reduced activation of T cells already present in the CNS, leading to apoptosis and strongly inhibits migration of activated T cells to the CNS and consequently lowers damage done to the CNS by these cells during Hu-PNS.

Study design

See primary and secondary outcomes

Intervention

Every 4 weeks, 300 mg natalizumab (Tysabri) will be i.v. infused over 1 hour, for a total of 3 infusions.

Natalizumab is used as monotherapy.

Concomitant immunotherapy will not be allowed with the exception of short courses of steroids.

Concomitant chemotherapy for an underlying malignancy will be allowed. PI will pay special attention to potential interaction with the study drug.

Contacts

Public
afdeling Neurologie, Erasmus MC,

P.A.E. Sillevis Smitt
‘s Gravendijkwal 230

Rotterdam 3015 GC
The Netherlands
010-7033327
Scientific
afdeling Neurologie, Erasmus MC,

P.A.E. Sillevis Smitt
‘s Gravendijkwal 230

Rotterdam 3015 GC
The Netherlands
010-7033327

Eligibility criteria

Inclusion criteria

- PEM/PSN associated with high titer (≥400) anti-Hu antibodies in serum or plasma

- The neurological symptoms must still be progressing defined as neurological deterioration over the last 4 weeks

- Score mRS ≥ 2

- Absolute CD4+ cell count ≥400 x 109 cells per liter

- Patients aged 18 years

- Patients who receive or will receive anti-tumor therapy are allowed to participate

- Patients who have given written informed consent

Exclusion criteria

- Patients who are unwilling to undergo lumbar puncture

- Known hypersensitivity to natalizumab or one of the additives

- Progressive multifocal leukoencephalopathy (PML)

- Immune compromised patients (patients using immunosuppressive medications other than short course (<2 weeks) of steroids)

- Liver enzymes (ASAT, ALAT, -GT, Alk. Phosphatase) higher than 5x upper limit of normal value (ULN)

- Chronic HBV infection (HBsAg positive)

- Renal failure (GFR < 30 ml/min)

- Active infection for which antibiotics are indicated

- Active viral infection for which antiviral medication is indicated

- Known current pregnancy or lactating (NB: women of childbearing potential should take adequate contraceptive precautions).

- No history of active melanoma in the past 5 years; no history of T cell lymphoma or primary CNS lymphoma

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-02-2016
Enrollment:	20
Type:	Anticipated

Ethics review

Positive opinion

Date:	07-02-2016
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 41883
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL5417
NTR-old	NTR5745
CCMO	NL48712.078.14
OMON	NL-OMON41883

Study results