Natalizumab (Tysabri®) for the treatment of anti-Hu associated paraneoplastic neurological syndromes

Published: 08-10-2015
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The primary objective of the study is the functional improvement with one point or more on the modified Rankin scale after the 12th week of natalizumab (compared to baseline).

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

Summary

ID

NL-OMON41883

Source
ToetsingOnline

Brief title
Tysabri in PNS

Condition

- Autoimmune disorders
- Central nervous system infections and inflammations

Synonym
Remote effects of cancer; paraneoplastic neurological syndrome

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,Biogen Idec International B.V.

Intervention

Keyword: Anti-Hu, Cancer, Natalizumab, Paraneoplastic neurological syndrome

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

Secondary endpoints include 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 12 weeks after last study drug administration.

Study description

Background summary

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. The most frequent PNS is associated with anti-Hu autoantibodies (Hu-PNS). Hu-PNS is a monophasic, severe, Th1 mediated organ specific autoimmune disease. 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. 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. 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 objective

The primary objective of the study is the functional improvement with one point or more on the modified Rankin scale after the 12th week of natalizumab (compared to baseline).

Study design

This is an uncontrolled single center phase II study testing 3 monthly infusions of natalizumab in 20 Hu-PNS patients.

Intervention

Natalizumab 300 mg, intravenous infusions q 4 weeks for a maximum of 3 infusions over 12 weeks.

Study burden and risks

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 Cancer Institute, location Daniel den Hoed Clinic. In addition, 2 lumbar punctures and 4 venapunctures are performed. The direct side effects of the 3 (maximum) natalizumab infusions are mild and manageable. 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. Potential serious side effects include PML and induction of tumor growth. However, the risk of these serious side effects is considered low.

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

- 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, g-GT, Alk. Phosphatase) higher than 5x upper limit of normal value (ULN)
- Chronic HBV infection (positive HBsAg)
- 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 phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-04-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tysabri
Generic name:	natalizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	08-10-2015
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-02-2016
Application type:	First submission
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

ID: 28171
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2014-000675-13-NL
CCMO	NL48712.078.14
OMON	NL-OMON28171