A Phase 3 Randomized, Rater- and Dose-Blinded Study Comparing Two Annual Cycles of Intravenous Low- and High-Dose Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta-1a (Rebif®) in Patients with Relapsing-Remitting Multiple Scleroris Who Have Relapsed On Therapy

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

Summary

ID

NL-OMON37217

Source
ToetsingOnline

Brief title
CARE MS-II

Condition

- Demyelinating disorders

Synonym
MS, Multiple Sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Genzyme
Source(s) of monetary or material Support: farmaceutical industry;sponsor

Intervention

Keyword: Alemtuzumab, Multiple Sclerose, Rebif, Relapse remitting MS (RRMS)

Outcome measures

Primary outcome

Primary endpoint will be time to SAD and relapse time.

The study will be considered to have met its primary efficacy objective if a statistically significant difference between the alemtuzumab treatment group and the interferon beta-1a group is observed for time to SAD or relapse rate. Confidence intervals and p-values will be presented for all primary efficacy endpoints for descriptive purposes regardless of the outcome of the Hochberg procedure.

The comparison of the SAD co-primary endpoint will use a Cox proportional hazards regression model with treatment group indicators, geographic region, and baseline EDSS as the only covariates in the model.

The comparison of the relapse rate co-primary endpoint will use the proportional means model. Treatment group indicators, geographic region, and baseline EDSS will be the only covariates in the model.

Supportive analyses will be performed using all of the available follow-up data, including data collected beyond Year 2, and will also include analyses restricted to Year 1 follow up.

Secondary outcome

The secondary endpoint are:

• Proportion of patients who are relapse free at Year 2.

• Change from baseline in EDSS.

• Acquisition of disability as measured by the MSFC.

• Percent change from baseline in MRI-T2 hyperintense lesion volume at Year 2.

Hypothesis testing for the secondary efficacy analyses will be performed using a closed testing procedure with the following rank order:

• Proportion of patients who are relapse free at Year 2.

• Change from baseline in EDSS.

• Acquisition of disability as measured by the MSFC.

• Percent change from baseline in MRI-T2 hyperintense lesion volume at Year 2.

The hypothesis testing will proceed from highest rank (1. Proportion of patients who are relapse free at Year 2) to lowest rank (4. Percent change from Baseline in MRI-T2 hyperintense lesion volume at Year 2), and if statistical significance is not achieved at an endpoint (p*0.05), then endpoints of lower rank will not be considered to be statistically significant. Confidence intervals and p-values will be presented for all

secondary efficacy endpoints for descriptive purposes, regardless of the

outcome of the closed testing procedure.

Study description

Background summary

This study will compare an investigational medicine, called alemtuzumab, to an approved medicine named Rebif® in people with early, active relapsing-remitting multiple sclerosis. Rebif® is an approved treatment for multiple sclerosis in the US, Canada, Australia, some South American countries and Europe.

Alemtuzumab (Campath/MabCampath) has been used as an experimental treatment of multiple sclerosis since 1991. Currently, alemtuzumab is approved to treat some types of leukemia but is not approved for the treatment of MS. As a leukemia treatment it is given more often and at much higher doses than in this study.

Approximately 400 MS patients have been treated with Alemtuzumab in clinical research studies conducted in Europe and the US. These studies have shown that it may be an effective treatment for multiple sclerosis. For instance, there has already been a study of alemtuzumab versus one of the standard treatments for multiple sclerosis, interferon beta 1a (Rebif®), in people with relapsing-remitting multiple sclerosis, study *CAMMS223*. This showed that two years* treatment with alemtuzumab, used at the dose proposed for this current study, reduced the risk of having a relapse, compared to Rebif®, by 72% and it also reduced the risk of acquiring sustained disability by 88% compared to Rebif®. But there were more side-effects associated with alemtuzumab compared to Rebif®.

We now want to conduct a large study comparing alemtuzumab and Rebif®, to carefully judge the balance between effectiveness and safety of alemtuzumab compared to interferon beta 1a.

Study objective

The objectives of this study are to compare the safety and efficacy of 2 annual cycles of intravenous (IV) alemtuzumab to 3-times weekly subcutaneous (SC) interferon beta 1a (Rebif*) in patients with active relapsing-remitting multiple sclerosis (RRMS) who have experienced at least 1 relapse while on disease-modifying drug therapy for *6 months.
To investigate these objectives, alemtuzumab will be compared to SC interferon beta-1a for efficacy in the time to sustained accumulation of disability (SAD), relapse rate, time to first relapse, acquisition of disability as measured by

changes in the Multiple Sclerosis Functional Composite (MSFC) plus visual function as measured by Sloan Charts, changes in magnetic resonance imaging (MRI)-T2 hyperintense lesion volume, other MS-related endpoints, and quality-of-life measures. Principal relapse analyses will be based on determinations of relapse made by an independent Relapse Adjudication Panel (RAP). Safety will be assessed by comparing alemtuzumab to SC interferon beta-1a for frequency and intensity of adverse events (AEs), changes in laboratory values for several hematologic and chemistry parameters, incidence of autoimmune disorders*especially immune thrombocytopenic purpura (ITP) and thyroid disorders*and incidence of infection.
The study will be considered to have met its efficacy objectives if a statistically significant treatment effect of alemtuzumab over SC interferon beta-1a is demonstrated in either or both of the co-primary efficacy endpoints: time to SAD and relapse rate.

Study design

This is a randomized study with a blinded rater, who performs the EDSS and MSFC tests with the patients. Approximately 573 eligible patients will be randomized 2:1. This is an open label study except for the blinded rater.

Intervention

Approximately 573 eligible patients will be randomized 2:1 to receive 2 annual cycles of IV alemtuzumab or 3-times weekly injections of SC interferon beta-1a for at least 2 years.

Alemtuzumab:
On Days 1, 2, and 3 of treatment (Month 0) and re-treatment (Month 12), all patients will receive premedication with 1 gram of IV methylprednisolone immediately prior to alemtuzumab infusion. Patients randomized to receive alemtuzumab will receive 12 mg/day for 5 consecutive days at Month 0 and for 3 consecutive days at Month 12. All alemtuzumab patients will also receive a course of acyclovir 200 mg twice daily (or therapeutic equivalent) beginning with the first day of each alemtuzumab cycle and continuing for 28 days after the last day of the cycle.

Rebif:
SC interferon beta-1a (44 mcg administered 3 times/week; a total 132 mcg/week) will be self- or other-administered by SC injection for the duration of the study period after the initial titration. Initial titration will occur over a 4-week period until the full dose of 44 mcg administered 3 times/week is reached. The titration schedule for SC interferon beta-1a is, per the labeling, 20% dose the first 2 weeks, 50% dose the next 2 weeks, reaching the full dose after 4 weeks of titration. The *Rebiject II** Rebif autoinjector may be used, but will not be provided by Genzyme.

On Days 1, 2, and 3 of treatment initiation (Month 0) and again at Month 12, SC interferon beta-1a-treated patients will receive premedication with 1 gram of IV methylprednisolone.

Study burden and risks

During the study the following non-invasive assessments will be conducted: neurological exams: a 500 meter walk, a timed 25 foot (7.63 meter) walk, a 9-hole peg test, an eye exam, and a test requiring you to add small numbers in your head quickly (Paced Auditory Serial Addition Test), yearly brain scans with MRI (Magnetic Resonance Imaging), monthly questionnaires to evaluate how you are feeling, to determine health condition, and to find out about other medical visits, standard urinalysis, physical examination and special neurological exams: Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC).

During the study the following invasive assessments will be done: monthly blood samples taken from a vein in your arm. Additional blood samples may be taken for medical testing.

The patients entering in the study may be subjected to the following invasive treatments: Alemtuzumab: 5 days in a row intravenous infusion for approximately 4-6 hours. 1 Year later 3 days intravenous infusion for approximately 4-6 hours. Rebif®: 3 times a week a subcutaneous injection for a minimum of two years, estimated between 2 and 3.5 years. Corticosteroids: 3 days infusion of methylprednisolone for approximately 1 hour every day, repeat after 12 months.

Treatment with Alemtuzumab may cause side effects: for a few hours, worsening of current or old symptoms from MS, rash in response to antihistamine medication, fever, headache, and fatigue - may last for a few hours, rigor/chills, nausea, vomiting, and/or diarrhea, shortness of breath and/or spasms in the windpipe, especially in patients with asthma, hypotension.
In addition, Alemtuzumab treatment may cause low platelet count, possibly leading to unusual bleeding, easy bruising, appearance of petechia Immune Trombocytopenic Purpura (ITP), easy bleeding of the gums, nosebleeds, and unusually heavy menstrual periods.
Alemtuzumab treated patients are at an increased risk of infections.
A small number, less than 1 %, of the patients who were treated with Alemtuzumab suffered from anti-glomerular basement membrane disease, anti-GBM or "Goodpasture*s disease".
Alemtuzumab treated patients may develop Graves* disease, an abnormality of the thyroid gland, with symptoms: increased sweating; anxiety; weight loss; tremor; and sometimes, pain in the neck.

Treatment with Rebif® may cause soreness, redness, pain, bruising, or swelling, and in some cases tissue necrosis, which may occur at the place of the injection. In addition, Rebif treatment may cause flu-like symptoms (fever,

chills, sweating, muscle aches, and fatigue) a few hours after each injection, but this side-effect usually disappears after a few weeks. Rebif treatment may also cause depression, liver problems, difficulty to fight an infection, tiredness or sluggishness, unusual bruising or bleeding, very rarely severe allergic reactions, leading to difficulty breathing and loss of consciousness, thyroid disease much less frequent than after alemtuzumab treatment but with similar symptoms.

The intravenous corticosteroid methylprednisolone may reduce or eliminate these symptoms, and antihistamine medication may further reduce the risk of rash. Methylprednisolone treated patients may experience nervousness and difficulty sleeping, which resolves within a day of the last infusion. Severe damage to bone, particularly the hip, is a rare side effect of high dose intravenous steroid treatment.

The acyclovir serves to prevent herpes virus infection and is generally well-tolerated. The most common side effects associated with acyclovir are nausea and diarrhea.

The MRI contrast agent gadolinium may cause mild headache, nausea and local pain, in less than 1% of the time low blood pressure and light-headedness occurs. Less than one in one thousand patients are allergic to the contrast agent, resulting in hives and itchy eyes, but more severe reactions have been seen, which result in shortness of breath.
Other than the risks of side effects, known or unknown, one disadvantage of this study is that you will be inconvenienced by blood tests, clinic visits, and MRI brain scans.
There may be other risks or side effects which are unknown at this time.

Contacts

Public
Genzyme

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

•Diagnosis of MS and MRI scan demonstrating white matter lesions attributable to MS
•Onset of MS symptoms within 10 years
•EDSS score 0.0 to 5.0
•>=2 MS attacks within 24 months, with >=1 attack within 12 months
•>=1 MS attack (relapse)during treatment with a beta interferon therapy or glatiramer acetate after having been on that therapy for at least 6 months within 10 years

Exclusion criteria

•Previous treatment with alemtuzumab
•Previous treatment with any investigational drug (i.e. a medication that is not approved at any dose or for any indication)
•Treatment with natalizumab, methotrexate, azothioprine or cyclosporine in the past 6 months
•Previous treatment with mitoxantrone, cyclophosphamide, cladribine, rituximab, or any other immunosuppressive, or cytotoxic therapy (other than steroid treatment)
•Any progressive form of MS
•Any disability acquired from trauma or another illness that could interfere with evaluation of disability due to MS
•Major systemic disease that cannot be treated or adequately controlled by therapy
•Active infection or high risk for infection
•Autoimmune disorder (other than MS)
•Impaired hepatic or renal function
•History of malignancy, except basal skin cell carcinoma
•Medical, psychiatric, cognitive, or other conditions that compromise the patient's ability to understand the patient information, to give informed consent, to comply with the trial protocol, or to complete the study

•Known bleeding disorder
•Of childbearing potential with a positive serum pregnancy test, pregnant, or lactating
•Current participation in another clinical study or previous participation in CAMMS323
•Previous hypersensitivity reaction to any immunoglobulin product
•Known allergy or intolerance to interferon beta, human albumin, or mannitol
•Intolerance of pulsed corticosteroids, especially a history of steroid psychosis
•Inability to self-administer subcutaneous (SC) injections or receive SC injections from caregiver
•Inability to undergo MRI with gadolinium administration
•Unwilling to use a reliable and acceptable contraceptive method throughout the study period (fertile patients only)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-06-2008
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NVT
Generic name:	Alemtuzumab
Registration:	Yes - NL outside intended use

Product type:	Medicine
Brand name:	Rebif
Generic name:	Interferon beta 1a
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-02-2008
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	06-05-2008
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	13-08-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	03-10-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	10-10-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	14-10-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

Approved WMO Date:	13-11-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	11-03-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	14-05-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	27-05-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	10-06-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	20-07-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	31-07-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	26-08-2009
Application type:	Amendment

Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	15-09-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	28-12-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	03-02-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	21-06-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	15-07-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	05-09-2011
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	28-09-2011
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

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	EUCTR2007-001162-32-NL
CCMO	NL21253.003.07
Other	not available