Efficacy of add-on high-dose simvastatin on markers for disease progression in MS patients treated with ocrelizumab and natalizumab (SIMSON), a phase II clinical trial.

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To assess the efficacy of add-on high-dose simvastatin on markers for disease progression in MS patients treated with natalizumab or ocrelizumab for at least six months.

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

Summary

ID

NL-OMON49976

Source
ToetsingOnline

Brief title
SIMSON trial

Condition

- Demyelinating disorders

Synonym
MS, Multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Stichting MS Research

Intervention

Keyword: Atrophy, MS, Progression, Simvastatin

Outcome measures

Primary outcome

The change in whole brain atrophy rate, comparing rates during 6-month run-in period to 18-month treatment period.

Secondary outcome

Secondary outcome measures include clinical outcome measures (neurological exam, arm- and walking functions, cognitive functions), biochemical outcome measures (sNfL, multi-parameter analysis of peripheral blood mononuclear cells (PBMC) and serum cholesterol), other imaging outcome measures (regional white and gray matter atrophy rate, functional connectivity on brain MRI, OCT), patient-reported outcome measures (questionnaires on the impact of MS on arm function, walking function, neuropsychological status and quality of life) and safety and tolerability (incidence of (serious) adverse events, CK levels).

Study description

Background summary

There are currently no satisfying therapeutic options for disease progression in multiple sclerosis (MS). The beneficial effects and favorable safety profile of statins are well established in cardiovascular disease. In the central nervous system, statins are shown to have cell-protective and anti-inflammatory properties. Previous studies in secondary progressive MS (SPMS) patients and

relapsing-remitting MS (RRMS) patients with first-line treatment showed that add-on high-dose statins were well tolerated and reduced atrophy rates and disability after 2 and 8 years respectively. The effect in a population with completely suppressed inflammation and on serum neurofilament light (sNfL) as a biomarker for disease progression remain unclear. The purpose of this single-center phase II clinical trial is therefore to investigate the efficacy of simvastatin in MS patients treated with natalizumab (NTZ) or ocrelizumab (OCR) for at least six months.

Study objective

To assess the efficacy of add-on high-dose simvastatin on markers for disease progression in MS patients treated with natalizumab or ocrelizumab for at least six months.

Study design

In this single-center investigator-initiated phase II clinical trial we choose to treat all subjects with the investigational product for 18 months and compare results to a run-in period of 6 months without treatment. Through this design, participants act as both subjects and controls and may all benefit from treatment. Moreover, the sample sizes that are needed to find differences between time points and subgroups remain limited. The occurrence of adverse events and the effect on clinical, biochemical and imaging measures will be closely monitored. Following informed consent, patients are screened for eligibility. Patients who meet inclusion criteria without exclusion criteria will start the 6 month run-in period without simvastatin. In month 7, patients will start simvastatin at a dosage of 40 mg a day and then escalate to high-dose treatment with 80 mg a day from month 8 to 24 (17 months). Patients will undero clinical, biochemical and imaging measures. Compared to our routine practice for patients treated with OCR or NTZ, the number of additional scans and measurements is limited.

Intervention

Add-on high-dose simvastatin 80 mg per day for 17 months (40 mg per day in month 7).

Study burden and risks

Simvastatin can be administered independently and proven safe and well tolerated for prevention of cardiovascular disease. Careful monitoring with blood samples every 3 to 6 months, yearly clinical measures, questionnaires and brain MRI is routine practice for MS patients treated in our center. Additional measures for this study include BICAMS, 6-MWTEC, functional MRI, OCT and 3 questionnaires. These are performed at baseline, month 6, month 12 and month

24. Routine laboratory tests are continued with additional serum cholesterol and CK monitoring. Adverse events survey is collected at every study and blood sample visit. The study schedule is designed in a way to limit the additional blood samples and visits compared to routine practice.

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

1. Definite diagnosis of multiple sclerosis (MS) according to the revised McDonald 2017 criteria.
2. Treatment with ocrelizumab or natalizumab for at least 6 months prior to inclusion.
4. Age 18 to 65 years old.

5. EDSS score 3.0 - 7.0 (inclusive).

Exclusion criteria

1. MS relapse within 6 months of baseline visit, with or without treatment with steroids.
2. Use of immunomodulation or -suppression other than ocrelizumab or natalizumab within the previous 6 months.
3. Commencement of treatment with fampridine within 3 months of baseline visit.
4. Concomitant use of lipid lowering drugs or use within 6 months before baseline visit.
5. Concomitant use of potent CYP3A4 inhibitors.
6. (History of) hypersensitivity, muscular toxicity or other adverse reaction due to statin or fibrate use.
7. Any predisposing factor to rhabdomyolysis: renal impairment (creatinine clearance <70 mL/min), uncontrolled hypothyroidism, personal or familial history of hereditary muscular disorders, alcohol abuse (>14 standard drinks units per week).
8. Baseline serum creatine kinase (CK) levels of >5 x ULN (confirmed by second measurement within 5-7 days), or at least 3-fold increase from baseline with associated muscle symptoms.
9. Active liver disease or unexplained persistent elevations of serum transaminases 3 x ULN.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	06-01-2020
Enrollment:	100
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	24-03-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2019-003127-38-NL
CCMO	NL71001.029.19