STOPPING OF DISEASE MODIFYING TREATMENTS AND OLIGOCLONAL BANDS IN PEOPLE WITH MULTIPLE SCLEROSIS

Published: 09-11-2020
Last updated: 09-04-2024

Primary Objective: • To compare the proportion of MS patients with OCBs between patients with and patients without recurrent disease 12 months after cessation of DMTs. Secondary Objectives: • To explore differences in CSF/ blood IgG indices between...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Autoimmune disorders
Study type	Observational invasive

Summary

ID

NL-OMON49527

Source
ToetsingOnline

Brief title
STOP-MS

Condition

- Autoimmune disorders
- Demyelinating disorders

Synonym
multiple sclerosis; MS

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,nog te werven

collectebusfonds;reserves MS centrum (vergoedingen voordrachten/ consultancy)

Intervention

Keyword: cerebrospinal fluid, disease modifying therapy, multiple sclerosis, oligoclonal bands

Outcome measures

Primary outcome

• Presence of CSF-unique oligoclonal bands (Y/N)

• Composite endpoint presence of inflammatory disease activity (all/one item Y

= Y; all N=N), consisting of:

o New T2 MRI white matter lesions at 1 year follow-up cerebral MRI scan (Y/N)

o Gadolinium-enhancing T1 MRI white matter lesions at 1 year follow-up cerebral

MRI scan (Y/N)

o The presence of a clinically clear exacerbation of disease with new

neurological symptoms lasting >24h and not suspect for a pseudo schub

Secondary outcome

• Number of CSF-unique oligoclonal band (N)

• Elevated intrathecal IgG production (Y/N)

• Cell count (N)

• CSF total protein level (concentration)

• CSF glucose (concentration)

• Number of new T2 MRI lesions at 1 year follow-up cerebral MRI scan (N)

• Number of gadolinium-enhancing T1 MRI lesions at 1 year follow-up cerebral

MRI scan (N)

• Sex (M / F)

• Year of birth (Y)

• Year of first symptoms (Y)

• Year of diagnosis (Y)

• Year of walking with stick (Y)

• Year of restricted to wheelchair (Y)

• Diagnosis (RRMS; SPMS; PPMS; not specified)

• Earlier lumbar puncture performed (Y/N)

• Year of earlier lumbar puncture (Y)

• CSF-unique oligoclonal bands present (Y/N/unknown)

• Disease modifying therapies used previously/ currently (descriptive)

• Comorbidities (descriptive)

• PDDS (step 0-8; Dutch translation attached)

• Worsening of walking last 5 years >= 1 point PDDS?

• Year of last relapse (Y)

• Adverse events (descriptive)

• Serious adverse events (descriptive)

Tertiary endpoints

• Proportions/ phenotypes B/ T cell subsets

• CSF levels of neurofilament light chain (NfL)/ soluble CD27 (sCD27)

Study description

Background summary

MS is een ontstekingsziekte van hersenen en ruggenmerg. Als ondersteuning voor de diagnose MS wordt vaak de activiteit van de intrathecale immuunrespons onderzocht door het meten van unieke oligoclonale banden (OCBs) in het hersenvocht. Deze OCBs worden bij diagnose bij >90% van de patienten gevonden, en voorspellen een inflammatoir actiever ziektebeloop van MS. Gedurende het natuurlijk ziektebeloop van MS neemt deze inflammatoire ziekteactiviteit bij de meest MS patienten af. Dit is moeilijk om te voorspellen. Er is een groot aantal ziektemodulerende therapieen (ZMTs) in MS, welke bij de aanwezigheid van inflammatoire ziekteactiviteit gestart worden. Wanneer ZMTs gestopt kunnen worden is veel onduidelijker. In verschillende opservationele studies ontwikkelt 50% (15-59%) van de patienten nieuwe ziekteactiviteit na stoppen van ZMTs. Voorspellers voor succesvol stoppen zijn een hoge leeftijd, en een langdurige afwezigheid van klinische aanvallen en MRI laesies.

Bij het Nederlands Herseninstituut onderzoeken we post-mortem hersenen van donoren met eindstadium MS. 78% van deze donoren heeft actieve ontstekingshaarden, met volop aanwezigheid van T cellen. Waar we in 92% van de diagnostische MS biopsie"en B cellen in laesies vinden, is dit in het eindstadium maar in 30% van de actieve laesies het geval. Donoren zonder B cellen in laesies toonden minder actieve laesies, minder T cel infiltratie en een milder ziektebeloop voor overlijden. We vonden dat donoren zonder be cellen in laesies of een lagere IgG productie in het hersenvocht hadden, met bij 30% afwezigheid van OCBs. We denken dat dit een reflectie van het natuurlijk beloop van het uitdoven van MS kan zijn: in ouderen met MS zien we uit klinische ervaring vaker afwezigheid van OCBs. Om te exploreren of oligoclonale banden gedurende het beloop van MS kunnen verdwijnen, hebben we in een cohort MS patienten met cognitieve klachten deze in een niet-diagnostisch hersenvochtmonster gemeten. OCBs waren afwezig in 20/74 (27%) deelnemers, waarbij we 6 casus konden identificeren waarbij ze verdwenen waren. Samangevoegd tonen deze data dat OCBs een dynamisch profiel gedurende MS kunnen hebben, en dat afwezigheid correleert met een minder inflammatoir pathologisch profiel bij autopsy.

Omdat leeftijd en klinisch/ radiologische ziekteactiteit onvoldoende sensitief zijn om hernieuwde ziekteactiviteit na stoppen van ZMTs te voorspellen, willen we onderzoeken of succesvol stoppen met ZMTs geassocieerd is met de afwezigheid van OCBs.

Study objective

Primary Objective:
• To compare the proportion of MS patients with OCBs between patients with and patients without recurrent disease 12 months after cessation of DMTs.

Secondary Objectives:
• To explore differences in CSF/ blood IgG indices between patients with and patients without recurrent disease 12 months after cessation of DMTs.

Tertiary Objectives:
• To explore differences in CSF/ circulating B and T cell subsets between patients with and patients without recurrent disease 12 months after cessation of DMTs.
• To explore differences in CSF and circulating soluble markers of MS disease activity (such as sCD27 and NfL) between patients with and patients without recurrent disease 12 months after cessation of DMTs.

Study design

This is a prospective 1 year cohort-study among people with MS under treatment at the outpatient clinic of our MS center ErasMS.

Study burden and risks

When evaluating candidates for cessation of MS DMTs in daily clinical practice, we usually make a cerebral MRI scan to confirm the absence of subclinical disease activity. When this is the case, and the decision is made to stop therapy, we follow-up patients for clinical signs of recurrent inflammatory disease activity. In case this is absent, or complaints are not sufficiently convincing of MS recurrence, we usually make a cerebral MRI scan after 12 months to evaluate subclinical disease activity. This is all accepted as standard of care in MS, and advocated by the recent concept guideline *Ziektemodulerende behandeling van Multiple Sclerose* (Dutch Society for Neurology).

Candidates to stop DMTs will be approached by their treating neurologist/ MS nurse about the trial, to ask their willingness to undergo a spinal tap for scientific research, and will receive the patient information folder. If the patient wishes to participate, in- and exclusion criteria will be checked, and the participant will receive an appointment at our outpatient clinic for the spinal tap.

At the outpatient clinic, a lumbar puncture with spinal tap will be performed according to local standard operating protocols. Approximately 5cc CSF and 5cc of serum will be sampled for determination of oligoclonal bands and IgG, additional 5cc CSF and 10cc blood will be sampled for biomarker analyses. Patients will be called one week after the spinal tap to follow-up eventual adverse events.

A lumbar puncture is frequently performed, and is in the absence of contraindications an unpleasant, yet relatively safe procedure. Patients will be carefully checked in advance for any contra-indications, and potential complications will be discussed, such as a low chance on hematomas with neurological deficits requiring neurosurgery, infections and post-punctional headache. A venous puncture can be regarded as painful and may result in a

hematoma.
The prospect of having a biomarker to assess inflammatory status of disease and possibly indication for stopping disease modifying treatments justifies exposing participants to the low risks as described above.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015GD
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Diagnosis MS according to Poser or any version of the McDonald criteria.
• Age >=45 years of age;
• Treatment with interferon beta, glatiramer acetate, dimethyl fumarate or teriflunomide;
• Absence of relapses within the previous 5 years;
• Absence of active MRI lesions (new T2 lesions compared to MRI <=2 years ago

OR gadolinium enhancing T2 lesions);
• Opportunity to provide written informed consent.

Exclusion criteria

• Use of oral anticoagulants OR clopidogrel as platelet aggregation inhibitor;
• Any other contra-indication for a lumbar punction;
• Unwillingness to undergo a lumbar and/or venous puncture.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-04-2021
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	09-11-2020
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

No registrations found.

In other registers

Register	ID
CCMO	NL73655.078.20