The safety and cost-effectiveness of discontinuing disease-modifying therapies in stable relapsing-onset multiple sclerosis (DOT-MS): a randomized rater-blinded multicenter trial.

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

Summary

ID

NL-OMON56344

Source
ToetsingOnline

Brief title
Discontinuation of disease modifying therapy in multiple sclerosis (DOT-MS)

Condition

- Demyelinating disorders

Synonym
multiple sclerosis

Research involving

Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Project goed gebruik geneesmiddelen van ZonMW,Stichting MS research

Intervention

Keyword: discontinuation of therapy, disease modying therapy, multiple sclerosis, safety

Outcome measures

Primary outcome

The primary endpoint is number of patients with return of inflammatory disease activity after 2 years based on: a clinically confirmed relapse (defined according to the definition most often used in MS phase-III trials: the onset of new or recurrent symptoms that last > 24 hours, that are accompanied by new objective abnormalities on a neurological examination and that are not explained by non-MS processes such as fever, infection, severe stress or drug toxicity (Gold et al NEJM 2012)) , or any emerging subclinical disease activity proven to be due to active disease/new inflammation (defined as 3 or more lesions on T2*weighted images or 2 or more gadolinium enhancing lesions on T1-weighted post-contrast MRI suggestive of demyelination) in the discontinuation group.

Secondary outcome

- Changes in neurological functioning: EDSS-change, MSFC-change (timed 25-foot walk test, 9-hole peg test, symbol digits modality test)
- Individual MRI-parameters: T1 post-contrast lesion numbers, T2 lesion numbers, atrophy measurements.

- Changes in quality of life measurements: MSIS-29, short form health survey (SF-36), CIS20r, MSSE, Treatment Satisfaction Questionnaire for Medication (TSQM), EQ5D-5L, iMCQ, iPCQ.

- Changes in biomarker measurements (neurofilament light).

- OCT and eye movement measurements: peri-papillary retinal nerve fiber (RNFL) thickness, macular ganglion cell-layer inner plexiform layer (GCL-IPL) thickness, eye movement measurements

- Changes in digital biomarkers using the NeuroKeys and MS sherpa mobile applications: 2-minute walking test, cognition test, questionnaire, keystroke data.

Study description

Background summary

The past few years, several new effective drugs have come onto the market for the treatment of relapsing remitting MS (RRMS), all of which have potentially serious side effects. The arrival of these drugs has led to a new aim for treating MS patients: achieving a status of complete clinical and radiological control of inflammatory events. With these adjusted goals, medication is often started at an earlier stage and the disease is treated more aggressively. This leads to better control of the disease, but also to increased exposure to possible (serious) side effects. A considerable group of patients with a fully stable-disease under treatment merely have a benign or less inflammatory disease course rather than a necessity for treatment to prevent inflammation. This raises the question whether and when patients who have been stable under medication for years can safely discontinue the treatment. The hypothesis of this study is that discontinuing medication after >5 years without evidence of inflammatory disease activity does not result in return of inflammatory disease activity.

Study objective

The aim of this study is to identify whether it is possible to safely discontinue treatment in stable RRMS patients who have shown no evidence of

active inflammation in the years prior to inclusion in terms of the return of inflammatory disease activity clinically and/or radiologically.

Primary research question:
- Can we safely discontinue first-line medication in long-term stable RRMS patients without the return of inflammatory disease activity clinically and radiologically?

Secondary research questions:
- Does the discontinuation of first-line treatment have an effect on disability progression?
- Does the discontinuation of first-line treatment improve the quality of life for the patient?
- What is the effect of discontinuation of first-line treatment on individual MRI outcome measures such as number of lesions and atrophy measurements?
- Is it possible to predict possible return of inflammatory activity with biomarkers such as neurofilament light (NFL) or patient characteristics such as disease activity prior to DMT?
- In case of emerging disease activity after cessation of DMT, will a restart of DMT result in NEDA again and if so, how long does it take?
- In case of emerging disease activity after treatment cessation, are there any differences between the different DMT compounds?
- Is discontinuation of first-line DMT associated with OCT measurements and eye movement measurements?
- Is it possible to detect and predict (return of) inflammatory disease activity and disease progression with digital biomarkers using mobile applications such as MS sherpa and Neurokeys?

Study design

Multi-center randomized and controlled, rater-blinded trial in the Netherlands. 130 patients with RRMS will be assigned to either discontinue the previously used disease modifying therapy (DMT) or to continue their DMT. Patients will be followed for 2 years, with the possibility to participate in an extension phase of the trial of 2 years.

Intervention

The intervention is the discontinuation of previously used disease-modifying therapy (DMT).

Study burden and risks

Patients in the continuation group and patients in the discontinuation group will be evaluated at baseline, after 3, 6, 12, 18 and 24 months. Evaluation

consists of clinical examination (EDSS and MSFC), radiological evaluation (MRI), questionnaires and serum samples. For patients in the Amsterdam UMC, OCT/Eyetracker measurements will be done at baseline, 3, 12 and 24 months. Current standard of care for MS-patients that use DMT's consists of a mininum evaluation frequency of once a year, mostly including MRI-scans. This means that patients in our study will be evaluated more frequently and more extensively than patients who receive standard clinical care. In addition, two mobile applications can be installed on the patients' smartphone (MS sherpa and Neurokeys). The MS sherpa application asks patients two complete three short tasks every two weeks, which take approximately 5 minutes to complete. Neurokeys replaces the patients' standard keyboard and collects data on the background during regular use of the smartphone.

The main risk of the intervention is return of inflammatory disease activity after discontinuing DMT. We will build in a safety-strategy (go-no-go strategy) to control for emerging disease activity (and patients safety). Interim analyses will be done after inclusion of the 40th, 70th and 100th patient. In both the continuation and discontinuation group, the proportion of patients that showed return of inflammatory disease activity - defined as an objectified MS relapse or 3 or more lesions on T2-weighted MRI-images or 2 or more gadolinium enhancing lesions on T1-weighted post-contrast MRI suggestive of demyelination - will be counted and compared between the treatment arms.

If there are more patients with return of inflammatory disease activity (according to the above mentioned definition) in the discontinuation group than in the continuation group, and the 95% confidence interval of the difference in the proportion of patients with return of disease activity between both groups does not include 0, we will discuss premature ending of the study with the DSMB.

For optimal safety the DSMB will monitor the decision making on premature termination every 3 months. The DSMB may advice to terminate the trial prematurely if disease activity exceeds above mentioned thresholds.

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

Patients who are treated with one of the first-line treatments (any of the interferons, glatiramer acetate, dimethylfumarate, teriflunomide) and who had a complete absence of inflammatory activity (no relapses, no new-T2 lesions and no contrast-enhancing lesions on MRI) for 5 consecutive years under first-line treatment will be eligible for inclusion. In case the last available MRI-scan was conducted 10 or more years ago, no more than 3 new T2-lesions in these 10 years are accepted.

Exclusion criteria

- Clinical or radiological inflammatory disease activity in the 5 years prior to the study.
- A switch between first-line disease modifying therapy over two years prior to inclusion, in case the switch has been due to in effectivity of the first DMT. In case the switch has been due to side-effects or by a personal preference of the patient (such as the wish to switch to oral therapies), this is not considered as an exclusion criterium.
3. Women who want to discontinue medication because of a pregnancy wish and women who are pregnant or expect to become pregnant during the study period
4. Patients that have previously used interferon-beta and have been tested positive for neutralizing antibodies (NAbs).

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Suspended
Start date (anticipated):	01-07-2020
Enrollment:	130
Type:	Actual

Medical products/devices used

Generic name:	digital biomarkers: mobile applications MS sherpa and Neurokeys
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	11-02-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-08-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2023
Application type:	Amendment
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
CCMO	NL71260.029.19