Immune regulation by dimethylfumarate (DMF) in patients with relapsing Remitting Multiple Sclerosis.

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Primary objective: * Increases treatment with DMF the ability of Tregs to inhibit in relapsing-remitting MS patients? Proliferation of conventional T cells * Provides treatment with DMF to an increase in the number of nTreg (Foxp3 expression) or...

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

Summary

ID

NL-OMON41017

Source
ToetsingOnline

Brief title
Dimethylfumarate by patients with MS

Condition

- Demyelinating disorders

Synonym
Multiple Sclerosis; MS

Research involving
Human

Sponsors and support

Primary sponsor: Orbis Medisch Centrum
Source(s) of monetary or material Support: Biogen Idec,Farmaceutische industrie

Intervention

Keyword: Dimethylfumarate, Multiple Sclerosis

Outcome measures

Primary outcome

-Effect of DMF treatment on Treg function as assessed in an in vitro, carboxyfluorescein succinimidyl ester (CFSE)-based proliferation suppression assay: to assess suppressive capacity of Tregs (CD4+CD25+CD127- T lymphocytes) we will use a proliferation suppression assay, in which responder T cells are cultured with varying amounts of T regs (Treg/Tresp ratio*s).(18;42) Treg normally suppress the proliferation of activated Tresps, but this pathway is defective in MS patients and might be restored by DMF.

-Effect of DMF treatment on Treg numbers as assessed by flow cytometry. After isolation, PBMC will be directly incubated with fluorescently labeled monoclonal antibodies which are directed against cell-subset-specific CD markers (CD4+CD25+CD127-FoxP3+)

-Effect of DMF treatment on Breg differentiation, i.e. IL-10 producing B cells after CpG stimulation: phenotypical analysis will be performed by intracellular flow cytometry, measuring frequencies of IL-10 producing B cells upon in vitro culture in the presence of CpG, a TLR-9 agonist.(23) The Breg frequency in MS patients is strongly reduced and may be restored by DMF treatment.

Secondary outcome

-T cell subset analysis based on intracellular cytokine expression as evaluated by flow cytometry (IL-10, IL-4, IL-17, IFN-*, TNF-* and GM-CSF); changes in the cytokine profiles will be associated with changes in Treg and Breg.

-Clinical outcome parameters such as the Kurtzke Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), relapse rate and Fatigue Scale for Motor and Cognitive Functions (FSMC) will be associated with changes in Treg and Breg.

Study description

Background summary

Although the exact pathophysiology of MS is uncertain, it is clear that the T cell compartment in here plays an important role. Autoreactive Th1 and Th17 cells in the central nervous system provide for inflammation. Regulatory T cells (Treg), which normally maintain the balance between pro-and anti-inflammatory T cells, are less effective in MS. Furthermore, it is now thought that B cells are important in the disease process. Clinical studies found that IL-10-producing B cells (Breg) also have regulatory properties. In our previous studies we found that MS patients have a decreased proportion Breg relative healthy subjects. Restore or stimulate both the Treg and Breg function seems a target in the treatment of MS.
Of different therapies for MS is indeed shown to exert their effects on Treg and / or Breg. However, DMF is a new therapy, whose mechanism of action is not well known. Through this study we investigate the mechanism of action of DMF is also based on effects on Treg and / or Breg.

Study objective

Primary objective:
* Increases treatment with DMF the ability of Tregs to inhibit in relapsing-remitting MS patients? Proliferation of conventional T cells
* Provides treatment with DMF to an increase in the number of nTreg (Foxp3 expression) or iTreg (IL-10 production) in relapsing remitting MS patients?
* Resulting treatment with DMF in an increase in Bregs, producing (more) of IL-10 in relapsing-remitting MS patients?

Secondary objective:
, Treatment with DMFals result in a shift of CD4 + T-cell cytokines to a less pro-and anti-inflammatory profile in relapsing-remitting MS patients?
* To assess the clinical outcome measures (EDSS, MSFC, relapse rate and FSMC) are associated with changes in patients treated with DMF. In Treg and Breg in relapsing-remitting MS

Study design

An observational study of 20 patients with RRMS who start Dimethylfumaratre. Patients will be treated with DMF as a regular patient. Ex vivo studies will be performed at 3 time points: prior to the start of the treatment with DMF, after 12 weeks and after 48 weeks of treatment with DMF.

Study burden and risks

Participating patients will have to participate in neurological examination and are asked to cooperate with neuropsychological tests. Besides that the assessments can be more or less fatiguing to the patients, there are no risks of these assessments. Finally, patients will donate blood. The risks of a blood donation are a temporary vasovagal reaction or a local haematoma at the puncture spot.

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

Relapsing Remitting Multiple Sclerose according to 2010 revised McDonald criteria
Age > 18 years
Disease duration < 5 years

Exclusion criteria

Relapse < 6 weeks prior to inclusion
Use of glucocorticosteriods < 6 weeks prior to inclusion
Use of disease modifying therapies in the past.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-12-2014
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	31-10-2014

Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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	NL50071.096.14