Supplementation of Vigantol oil versus placebo as Add-on in patients with relapsing remitting multiple sclerosis receiving Rebif treatment (immune modulating effects of vitamin D3)

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

Summary

ID

NL-OMON34565

Source
ToetsingOnline

Brief title
SOLAR(IUM) - an immunological sub-study of the SOLAR study

Condition

- Demyelinating disorders

Synonym
multiple sclerosis; MS

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W,Ondersteuning aangevraagd bij MS Research Stichting/ Nationaal MS Fonds

Intervention

Keyword: immune system, multiple sclerosis, T cells, vitamin D

Outcome measures

Primary outcome

• Difference in distribution of cytokine profile of peripheral CD4+ T

lymphocytes by flowcytometry at Week 48 between treatment arms

Secondary outcome

• Difference in distribution of results from phenotypic analysis of T and B

lymphocyte subsets by flowcytometry at Week 48 and Week 96 between treatment

arms;

• Difference in distribution of results from functional analysis of cytokine

production (flowcytometry and ELISA assays) by T and B lymphocytes at Week 48

and Week 96 between treatment arms;

• Differences in distribution of circulating levels of immune-related

regulatory molecules at Week 48 and 96 between treatment arms;

• Difference in evolution in time of immune-parameters described above between

the treatment arms;

• Correlation of the distribution of results from the analyses above with serum

levels of 25-hydroxyvitamin D in all participants, as are collected in the

SOLAR(IUM) study;

• Difference in distribution of results from the analyses above between

patients from the vitamin D3 supplementation arm which did or did not respond clinically to vitamin D3 supplementation (i.e. remained relapse free in the SOLAR trial at week 96/ No signs of disease activity on MRI);

• Difference in distribution of results from the analyses above between carriers of relevant genetic polymorphisms as are studied in the SOLAR trial, including MHC class II region (HLA-DRB15*01) and the vitamin D metabolism genes (VDR and CYP27B1).

Study description

Background summary

Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system (CNS). Naïve T cells are primed in the periphery and mgrate as auto-reactive T cells to the CNS, where they contribute to an inflammatory reaction against the myelin sheaths surrounding neurons. A poor vitamin D status has been associated with an increased risk on developing MS (Ascherio et al. Lancet Neurol 2010), and with an increased disease activity of MS (Simpson et al. Ann Neurol 2010; Mowry et al. Ann Neurol 2010; Smolders et al. Mult Scler 2008). To assess the efficacy of high dose vitamin D3 supplementation as add-on treatment in patients with MS, we designed the SOLAR trial.

The mechanism by which vitamin D could modulate the disease course of MS is unknown, but most researchers think that the central involvement of vitamin D in the regulation of the adaptive immune response plays a critical role in this association. In experimental research, in vitro and in animal models of MS, vitamin D appears to be an important promoter of T cell homeostasis (Smolders et al. J Neuroimmunol 2008). In a cross-sectional study among MS patients, we found in patients with a poor vitamin D status less functional regulatory T cells and a Th1/Th2 balance which was more shifted towards Th1 (Smolders et al. PLoS One 2009). A phase 1/2 study (Burton et al. Neurology 2010) and a pilot study (Smolders et al. PLoS One 2010) suggested that supplementation of high doses of vitamin D could shift the T cell compartment in a less pro-inflammatory direction.

Study objective

The primary objective of this study is to assess whether the CD4+ T cell compartment displays a less pro-inflammatory profile in patients which are supplemented for the SOLAR study with high doses of vitamin D3 when compared to patients which are supplemented for the SOLAR study with placebo.

Study design

This is a blinded observational study among participants of the SOLAR study. Participants of SOLAR are randomized over 2 treatment arms: either 96-weeks supplementation of high doses of vitamin D (4 weeks 7.000 IU/d; 92 weeks 14.000 IU/d), or 96 weeks supplementation of placebo. The peripheral immune compartment will be assessed at week 0, week 48, and week 96. After the last analysis of the last patient, the database will be locked and de-blinding will occur. The difference in distribution of immune parameters between the groups at week 48 and 96 will be assessed.

Study burden and risks

At given time points, blood is drawn from the participants for de SOLAR trial. For the SOLAR(IUM) study, a total volume of 10 mL will be added to this sampling at given time points (week 0, 48, and 96). There is no need for additional sampling. The risk of this addition for the wellbeing of participant is negligibly small. The risks of blood withdrawal are a transient vasovagal collaps ('fainting'), and/or getting a local haematoma.

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

In short, the only inclusion criteria are: i) matching the inclusion criteria of SOLAR, ii) willing to provide additional informed consent for the SOLAR(IUM) study. The inclusion most prominent criteria of SOLAR are:
• Males and females between 18 and 50 years of age.
• Diagnosis of a relapsing-remitting form of MS, according to the revised McDonald criteria 2005
• Brain and/or spinal MRI with findings typical of MS.
• A first clinical event occurring within 5 years prior to Screening.
• Disease activity characterized by: at least one MS lesion within the 12 months prior to Screening, or ne or more Gd-enhancing MRI lesions within the 12 months prior to Screening.
• EDSS score <= 4.0 at Screening.
• Currently and for the first time treated with interferon-beta-1a (tiw) s.c., and having received this treatment for a minimum of 90 days and for not longer than 12 months before baseline visit (including titration period).
• Willingness and ability to comply with the protocol for the duration of the trial.
• Written informed consent given prior to any trial-related procedure not part of the normal medical practice.

Exclusion criteria

Te only exclusion criterion of SOLAR(IUM) is matching any exclusion criterium of SOLAR. The most prominent exclusion criteria of SOLAR are:
• Pregnancy and lactation period
• Any disease other than MS that could better explain signs and symptoms.
• Complete transverse myelitis or bilateral optic neuritis.
• Currently receiving or use at any time of monoclonal antibodies, mitoxantrone, cytotoxic or immunosuppressive therapy.
• Use of any cytokine or anti-cytokine therapy, intravenous immunoglobulin, plasmapheresis, or any investigational drug or experimental procedure within 12 months prior to Screening.
• Use of oral or systemic corticosteroids or ACTH within 30 days prior to the SD1 visit.
• Have experienced a relapse within 30 days before the SD1 visit

• Have abnormalities of Vitamin D related hormonal system other than low dietary intake or decreased sun exposure, i.e. primary hyperparathyroidism or granulomatous disorders.
• Have an urine calcium/creatinine (mmol/mmol) ratio greater than 1.0 or hypercalcaemia (11 mg/100cc (5.5 mEq./l.).
• Are taking medications that influence Vitamin D metabolism other than corticosteroids, e.g., phenytoin, barbiturates, thiazide diuretics and cardiac glycosides.
• Are taking more than 400 IU (10 µg) of Vitamin D supplement daily.
• Have conditions with increased susceptibility to hypercalcaemia, e.g., known arrhythmia or heart disease, treatment with Digitalis, or Hydrochlorothiazide and those who suffer from nephrolithiasis.
• Have inadequate liver function, defined by alanine aminotransferase (ALT) > 3 times upper limit of normal (ULN), aspartate aminotransferase (AST) > 3 times upper limit of normal (ULN)or alkaline phosphatase > 2.5 times ULN, or total bilirubin > 1.5 times ULN, if associated with any elevation of ALT or alkaline phosphatase
• Moderate to severe renal impairment
• Inadequate bone marrow reserve, defined by a WBC count < 0.5 times the lower limit of normal.
• History or presence of serious or acute heart disease
• History or presence of severe depression, history of suicide attempt, or current suicidal ideation.
• Epilepsy or seizures not adequately controlled by treatment.
• Current or past (within the last 2 years) alcohol or drug abuse.
• Any major medical or psychiatric illness (such as psychosis, bipolar disorder) that in the opinion of the Investigator could create undue risk to the subject or could affect adherence with the trial protocol.
• Known contra-indication to treatment with vitamin D (according to SPC)
• Known hypersensitivity to IFN or its excipient(s) (according to SPC).
• Known hypersensitivity to gadolinium.
• Any other condition that would prevent the subject from undergoing an MRI scan.

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-05-2011
Enrollment:	42
Type:	Actual

Ethics review

Approved WMO

Date:	08-02-2011
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	NL35094.096.10