Fluoxetine therapy in Multiple Sclerosis. A double blind, randomised, placebo-controlled, phase II study in patients with relapsing Multiple Sclerosis.

Gepubliceerd: 15-09-2005 Laatst bijgewerkt: 18-08-2022

The hypothesis is that MS is a T cell-mediated autoimmune demyelinating disease of the central nervous system (CNS). In order to start immune reactions in the CNS, myelin antigen need to be presented on the surface of antigen presenting cells (APCs...

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON23750

Bron
Nationaal Trial Register

Verkorte titel
N/A

Aandoening

Relapsing multiple sclerosis.

Ondersteuning

Primaire sponsor: Multiple Sclerosis Internationaal, Amsterdam, The Netherlands
Overige ondersteuning: Innovatiefonds UMCG

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Difference between Week 0 and Week 24 in the cumulative number of active lesions on MRI scans.

Toelichting onderzoek

Achtergrond van het onderzoek

In this double blind, randomised, placebo-controlled, phase II study the effect of fluoxetine on disease activity of patients with multiple sclerosis was tested.

Doel van het onderzoek

The hypothesis is that MS is a T cell-mediated autoimmune demyelinating disease of the central nervous system (CNS). In order to start immune reactions in the CNS, myelin antigen need to be presented on the surface of antigen presenting cells (APCs) in conjunction with MHC class II molecules, and this antigen-MHC II complex needs to be recognized by a specific T cell receptor (TCR) of the anti-myelin T cells. The neurotransmitter norepinephrine inhibits interferon gamma-induced MHC class II antigen expression on astrocytes in vitro through ß2 adrenergic signal transduction mechanisms. We found that astrocytes in MS lack ß2 adrenergic receptors (Neurology 1999;53:1628-33; Neurosci Lett 2000;298:75-7). We hypothesize that a loss of these receptors in MS facilitate the deviation of astrocytes to function as facultative immunocompetent antigen presenting cells (Arch Neurol 2003; 60:132-6). In support of this, we were able to demonstrate that reactive astrocytes in MS lesions express MHC class II and B7-costimulatory molecules, and are therefore equipped to promote APC-dependent T cell activation (Neuroreport 2000;11:89-91; J. Neuroimmunol 2002;136:166-71).
Compounds that elevate cAMP in astrocytes may restore suppression of MHC class II molecules in astrocytes.

We investigated other aminergic receptors on astrocytes in MS and found some receptors that are also linked to the regulation of intracellular cAMP formation. An interesting candidate receptor is the 5-HT4 receptor. We intended to start a clinical study in patients in MS with the 5-HT4 agonist cisapride. However, we abandoned this project because of recent serious safety concerns with cisapride.
Astrocytes also contain the 5-HT transporter. Drugs that block this transporter elevate endogenous serotonin concentrations, and it has been shown that serotonin also increases cAMP levels in cultured astrocytes (J Neurosci Res 2001;64:261-7). Fluoxetine is a prototype drug that can be used to achieve this goal.Fluoxetine is occasionally used in patients with MS who are depressed. One investigator (Traugott) noticed that patients using fluoxetine seemed to stabilize with respect to their MS-related symptoms.

She also found a beneficial effect of fluoxetine in an animal model of MS, chronic relapsing experimental allergic encephalitis (http://www.albany.net/~tjc/fluoxetine-ms.html).

The aim of this clinical trial is to assess the effects of fluoxetine, a 5-HT transporter blokker, on disease activity in patients with MS. The drug is well tolerated and is off patent.

Onderzoeksopzet

N/A

Onderzoeksproduct en/of interventie

Fluoxetine capsule 20 mg/ day orally versus placebo. Medication is taken from week 0 to 24.

MRI scans are performed at week -4, 0, 4, 8, 16 and 24.

EDSS, MSFC and questionnaires are assessed at week 0 and 24.

Contactpersonen

Publiek

University Medical Center Groningen (UMCG),
P.O. Box 30001
J.P. Mostert
Hanzeplein 1
Groningen 9700 RB
The Netherlands
+31 (0)50 3614817 / +31 (0)50 3612430

Wetenschappelijk

University Medical Center Groningen (UMCG),
P.O. Box 30001
J.P. Mostert
Hanzeplein 1
Groningen 9700 RB
The Netherlands
+31 (0)50 3614817 / +31 (0)50 3612430

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Written informed consent;

2. Male and female patients aged 18 to 65 years inclusive;

3. Confirmed diagnosis of MS, as defined by the McDonald criteria;

4. Relapsing remitting or relasping secondary progressive MS, as defined by the Lublin Criteria;

5. At least one documented clinical or subclinical (defined as a gadolinium enhanced lesion on MRI examination) exacerbation in the last year
or 2 documented exacerbation’s in the last 2 years (one of which can be subclinical)
or the presence of one gadolinium enhanced lesion on the Week-4 MRI scan;

6. Baseline Expanded Disability Scoring Scale (EDSS) score of 0.0-6.0 inclusive.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Intolerance or contraindications to MRI scanning;

2. Abnormal MRI scan, not attributable to MS;

3. Neurological disorder other than MS, acute or chronic infection, malignant neoplasm or metastasis, cardiovascular disorder or pulmonary disorder, severe intercurrent systemic disease, or any other disease that interferes with the assessments;

4. Treatment with interferon ß, glatiramer acetate, plasmapheresis, other immunomodulatory drugs, or immunosuppressive drugs including azathioprine, cyclophosphamide and methotrexate, within 6 months of week 0;

5. Treatment with systemic corticosteroids in the 30 days prior to Week -4, or between Week -4 and Week 0;

6. Women of childbearing potential, who are not using a medically accepted safe method of contraception (medically acceptable safe methods of contraception for the purposes of this study will include surgical sterilisation, oral or depot contraceptives [taken for at least 60 day before Week 0], intrauterine devices, diaphragm with spermicidal; other methods, i.e. sexual abstinence may be considered by the
Investigator as appropriate contraception on a patient-by-patient basis);

7. Pregnancy or women who are lactating;

8. Moderate to severe depression measured as a score > 18 on the Beck Depression Inventory;

9. Bipolar disorder;

10. Treatment with antidepressant medications (SSRI, TCA, other) and/or lithium.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-01-2004
Aantal proefpersonen:	40
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	15-09-2005
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL375
NTR-old	NTR415
Ander register	: N/A
ISRCTN	ISRCTN65586975

Resultaten

Samenvatting resultaten
J Neurol Neurosurg Psychiatry. 2008 Sep;79(9):1027-31. Epub 2008 May 1.