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

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23750

Source
Nationaal Trial Register

Brief title
N/A

Health condition

Relapsing multiple sclerosis.

Sponsors and support

Primary sponsor: Multiple Sclerosis Internationaal, Amsterdam, The Netherlands
Source(s) of monetary or material Support: Innovatiefonds UMCG

Intervention

Outcome measures

Primary outcome

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

scans.

Secondary outcome

1. Difference between Week 0 and Week 24 in:

a. Tthe change in lesion volume on T2 weighted MRI;

b. The change in gadolinium-enhanced lesion volume on Tl weighted MRI;

2. Difference in the number of MS exacerbations over the 24-week period.

3. Difference in the change in EDDS, Multiple sclerosis Functional Composite (MSFC), Fatigue severity scale, and QoL (SF 36) between Week 0 and Week 24
The MSFC comprises quantitative functional measures of three key clinical dimensions of MS: leg function/ambulation (Timed 25-Foot Walk), arm function (Nine-Hole Peg Test), and cognitive function (Paced Auditory Serial Addition Test [PASAT]). Scores on component measures are converted to standard scores (z-scores), which are averaged to form a single MSFC score.

Study description

Background summary

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

Study objective

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.

Study design

N/A

Intervention

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.

Contacts

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Eligibility criteria

Inclusion criteria

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.

Exclusion criteria

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.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2004
Enrollment:	40
Type:	Actual

Ethics review

Positive opinion

Date:	15-09-2005
Application type:	First submission

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
NTR-new	NL375
NTR-old	NTR415
Other	: N/A
ISRCTN	ISRCTN65586975

Study results

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