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Fluoxetine therapy in multiple sclerosis: a double blind, randomised, placebo-controlled, phase II study in patients with relapsing multiple sclerosis

Submission date
27/01/2006

Recruitment status
No longer recruiting

Registration date
27/01/2006

Overall study status
Completed

Last Edited
03/07/2009

Condition category
Nervous System Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
NTR415

Study information

Scientific Title

Study objectives
The hypothesis is that multiple sclerosis (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 needs 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 recognised 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. We hypothesise that a loss of these receptors in MS facilitate the deviation of astrocytes to function as facultative immunocompetent antigen presenting cells. 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.

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

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from the local medical ethics committee

Study design
Double blind, randomised, placebo-controlled, parallel group phase II study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Multiple sclerosis (MS)

Interventions

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

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Fluoxetine

Primary outcome(s)
Difference between week 0 and week 24 in the cumulative number of active lesions on MRI scans.

Key secondary outcome(s))
1. Difference between Week 0 and Week 24 in:
1.1. The change in lesion volume on T2 weighted MRI
1.2. 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 (36-item short form health survey [SF-36]) between week 0 and week 24. The MSFC comprises quantitative functional measures of three key clinical dimensions of MS:
3.1. Leg function/ambulation (timed 25-Foot Walk)
3.2. Arm function (Nine-Hole Peg Test)
3.3. 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.

Completion date
01/07/2006

Eligibility

Key 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 relapsing secondary progressive MS, as defined by the Lublin Criteria
5. At least one documented clinical or subclinical (defined as a gadolinium enhanced lesion on magnetic resonance imaging [MRI] examination) exacerbation in the last year or two documented exacerbations 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

Participant type(s)

Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key 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 greater than 18 on the Beck Depression Inventory
9. Bipolar disorder
10. Treatment with antidepressant medications (selective serotonin reuptake inhibitors [SSRI], tricyclic antidepressant [TCA], other) and/or lithium

Date of first enrolment
01/01/2004

Date of final enrolment
01/07/2006

Locations

Countries of recruitment
Netherlands

Study participating centre
University Medical Center Groningen
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Sponsor information

Organisation
University Medical Center Groningen (UMCG) (Netherlands)

ROR
https://ror.org/03cv38k47

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
University Medical Center Groningen (UMCG) (Netherlands) - Innovatiefonds

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	Results	01/09/2008		Yes	No