Simvastatin addition to improve symptoms, cognition, metabolic syndrome and movement disorders in patients with recent-onset psychotic disorder.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolism disorders NEC
Study type	Interventional

Summary

ID

NL-OMON47934

Source
ToetsingOnline

Brief title
Simvastatin in patients with recent-onset schizophrenia.

Condition

- Metabolism disorders NEC
- Schizophrenia and other psychotic disorders

Synonym
Schizophrenia; psychosis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: The Stanley Medical Research Institute en TOP Grant ZonMw

Intervention

Keyword: metabolic syndrome, psychosis, simvastatin, symptoms

Outcome measures

Primary outcome

Main study parameter is symptom severity as measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987). We will compare the effect of simvastatin versus placebo, both given in addition to antipsychotic medication, with regards to change in symptom severity expressed as overall PANSS score after 12 months of treatment. In addition, we will examine neurocognitive functioning as measured with the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al. 2004).

Secondary outcome

Our secondary study parameters are the PANSS subscales: the positive scale, negative scale and general psychopathology scale. Furthermore, general assessment of functioning will be evaluated using the Global Assessment of Functioning scale (GAF; Jones et al. 1995), presence and severity of metabolic syndrome as defined by the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLB; Grundy et al. 2005), and presence and severity of movement disorders using validated scales. MRI will be used to investigate changes in the structural properties of the brain. These parameters will be

compared after 12 months of treatment, between patients treated with simvastatin versus placebo. Other parameters are severity of depression as assessed with the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al. 1993) and experience of childhood trauma will be evaluated with the Childhood Trauma Questionnaire Short Form (CTQ-SF). In addition, in order to investigate immunological and metabolic biomarkers that predict treatment response to simvastatin therapy, serum, peripheral blood mononuclear cells (PBMC) and RNA of all patients will be analyzed.

Study description

Background summary

There is ample evidence that inflammatory processes play a role in the pathophysiology of schizophrenia. Although Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been shown to be able to reduce symptoms in these patients (reviewed by Sommer et al. 2012), these drugs either have unfavourable cardiovascular side effects or are otherwise not well tolerated (Solomon et al. 2005). Moreover, patients with schizophrenia already tend to have an increased cardiovascular risk (Hennekens et al. 2005). The combination of well-established vascular protection and reduction of inflammation by simvastatin (Orr et al. 2008) offers a highly attractive potential to further improve the treatment of schizophrenia and related disorders.

Study objective

The primary objective of this trial is to investigate the proposed beneficial effect of simvastatin on total symptom severity (PANSS) as compared to placebo when given in addition to antipsychotic medication, and the effects on neurocognitive functioning as measured with the Brief Assessment of Cognition in Schizophrenia (BACS).Secondary objectives concern assessment of positive and negative symptoms as well as general psychopathology (PANSS subscales), in addition to general functioning using the GAF (Global Assessment of Functioning), presence and severity of metabolic syndrome as defined by the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLB), changes in the brain using MRI, and presence and severity of movement disorders

using validated scales. Various immunological and metabolic parameters will be assessed in blood samples to examine whether these parameters predict treatment response to simvastatin augmentation, as well as an assessment of childhood trauma (Childhood Trauma Questionnaire-Short Form; CTQ-SF). In addition, severity of depression will be assessed using the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al. 1993). Finally, safety data will be evaluated by comparing incidences (number and % of subjects with at least one occurrence) of key SAEs and SUSARs between both groups, e.g. hospitalisations.

Study design

Randomized multi-centre placebo-controlled double-blind trial.

Intervention

Patients will be randomized 1:1 to either 40 mg simvastatin or placebo daily, in the form of identical tablets.

Study burden and risks

Use of simvastatin implies that there is a risk of side effects, as all lipid-lowering drugs carry the risk of negative effects. The number of patient visits will be limited and mainly requires time investment for a few physical examinations, questionnaires and two cognitive testing sessions (around 16 hours in total during the treatment period of 1 year and the follow-up visit 24 months post baseline). Blood will be drawn at six occasions with negligible and known risks (e.g. irritation). The two magnetic resonance imaging (MRI) scan sessions are not associated with any known risks. The burden and risks are acceptable while the benefits are expected to be considerable.

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

A DSM-IV-R diagnosis of: 295.x (schizophrenia, schizophreniform disorder, or schizoaffective disorder) or 298.9 (psychosis NOS);
Onset of first psychosis no longer than 3 years ago;
Age between 18 and 50 years;
Written informed consent is obtained;
Female patients of childbearing potential need to utilize a proper method of contraception (the pill, vaginal ring, hormonal patch, intrauterine device, cervical cape, condom, contraceptive injection, diaphragm) in case of sexual intercourse during the study.

Exclusion criteria

Fulfilment of criteria for statin prescription; according to the Dutch Heart Foundation (Hartstichting), statin treatment is indicated when the total cholesterol level is > 8 mmol/l (www.hartstichting.nl);
Presence of any of the contra-indications or warnings for the use of simvastatin as reported in the SPC;
Chronic use of glucocorticosteroids (temporary use is permitted, if stopped at least 1 month before start of treatment trial);
Chronic use of non-steroidal anti-inflammatory drugs (temporary use is permitted, if stopped at least 1 month before start of treatment trial);
Current use of statins or other lipid-lowering drugs (temporary use is permitted, if stopped at least 1 month before start of treatment trial);
Pregnancy or breast-feeding (urine pregnancy test will be performed for sexually active females with child bearing potential);
In case of familial risk for muscular disorders or previously experienced muscle toxicity when taking medication similar to simvastatin, creatine kinase (CK) levels will also be checked (as recommended by the Dutch Farmacotherapeutisch Kompas,

www.farmacotherapeutischkompas.nl/);
In addition, levels of aspartate (ASAT), alanine aminotransferase (ALAT), gamma-glutamyltranspeptidase (gamma-GT) and creatinine will be checked when a history of alcohol abuse, liver or kidney disorders is reported based as recommended by the Dutch Farmacotherapeutisch Kompas, www.farmacotherapeutischkompas.nl/);
Use of comedication that either inhibits or induces the live enzyme CYP3A4 which is responsible for the degradation of simvastatin. Inhibitors of CYP3A4 include itraconazole, ketoconazole, posaconazole, fluconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, telaprevir, boceprevir, imatinib, ticagrelor, voriconazole; inducers of CYP3A4 include carbamazepine, efavirenz, nevirapin, etravirin (can be washed out before start of trial);
Use of comedication that may increase the risk for myalgia, rhabdomyolyse and myopathy, including colchicine, bosentan, fenobarbital, fenytoin, hypericum, rifabutin, rifampicin, fibrates (e.g. gemfibrozil), fusidic acid, carbamazepine (can be washed out before start of trial). The MRI scan requires additional exclusion criteria to be eligible to participate in this part of the study (if these additional criteria are met, patients can participate in the study but not in the MRI component): Ferrous objects in or around the body (e.g. braces, glasses, pacemaker, metal fragments) Claustrophobia

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-11-2013
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.v.t.
Generic name:	Simvastatin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-06-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-09-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Not approved Date:	14-01-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-02-2015
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
Other	ClinicalTrials.gov identifier: NCT01999309
EudraCT	EUCTR2013-000834-36-NL
CCMO	NL43806.041.13