BBA Clinical 4 (2015) 52–58

Contents lists available at ScienceDirect

BBA Clinical

journal homepage: http://www.journals.elsevier.com/bba-clinical/

Simvastatin augmentation for recent-onset psychotic disorder: A study protocol

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ARTICLE INFO

Article history:
Received 22 April 2015
Received in revised form 16 June 2015
Accepted 28 June 2015
Available online 3 July 2015

Keywords:
Anti-inflammatory
Schizophrenia spectrum disorders
Psychosis
Simvastatin
Treatment
MRI

ABSTRACT

Background: There is ample evidence that inflammatory processes play a role in the pathophysiology of schizophrenia. Randomized controlled trials have shown benefit of some (but not all) anti-inflammatory drugs on symptom severity. So far, these drugs have been given for a relatively short period. Simvastatin combines well-established vascular protection with reduction of the inflammatory status of the brain, thus offering an attractive potential to further improve treatment of schizophrenia and related disorders.
Methods/design: We are currently undertaking a double-blind placebo-controlled trial, including 250 patients (18–50 years of age) whom are diagnosed with a schizophrenia spectrum disorder. Onset of their first psychosis should be no longer than three years ago. Patients are randomized 1:1 to either 40 mg simvastatin or placebo daily during one year, next to their regular antipsychotic treatment. Primary outcome measures are symptom severity and cognitive decline as measured by the Positive and Negative Syndrome Scale (PANSS) and Brief Assessment of Cognition in Schizophrenia (BACS), at baseline and end of treatment. Secondary aims are to establish an attenuation of brain tissue loss and an improvement in general functioning, presence and severity of metabolic syndrome and degree of movement disorders. Lastly, immunological and metabolic parameters are assessed in blood samples to possibly predict treatment response.
Discussion: We hypothesize simvastatin to lower symptom severity and to prevent or reduce excessive brain tissue loss and cognitive decline, compared to placebo. We expect that simvastatin will be well-tolerated and lead to decreased prevalence of metabolic syndrome.
Trial registration: ClinicalTrails.gov NCT01999309; EudraCT-number 2013-000834-36.

1. Introduction

Although the introduction of antipsychotic medications in the 1950s has substantially improved clinical symptoms of schizophrenia [32], the disease is still causing considerable morbidity and mortality [28]. Different lines of evidence now suggest that low-grade inflammation in the central nervous system is involved in the pathogenesis of schizophrenia, possibly affecting a specific subgroup of patients. These include the increased risk of schizophrenia patients and their relatives for specific auto-immune diseases [6], clinical similarities between the course of schizophrenia and auto-immune disease [23] and decreased prevalence of schizophrenia in men who have used non-steroidal anti-inflammatory drugs (NSAIDs) [24] or glucocorticosteroids [25] for somatic disorders. Furthermore, an infectious cause or trigger is suggested by the observed association between schizophrenia and pre- and perinatal infections [10], as well as by seroconversion to certain pathogens in patients with schizophrenia [33].

The case of this increased inflammation is most likely both genetic and environmental. A large pooled data-set of single nucleotide polymorphism (SNP)-based genome-wide association studies followed up the most significant association signals [31]. One of the most remarkable findings was a significant association with several markers spanning the major histocompatibility complex (MHC) region on chromosome 6p21.3–22.1. This genetic deviation in the MHC region is consistent with an immune component to schizophrenia risk. Furthermore, recent studies suggest that negative environmental influences such as childhood trauma and drug abuse affect the brain by increasing the inflammatory response [1,7].

On a cellular level, inflammation of the central nervous system is suggested by an increased number of activated microglia cells in the brains of patients with recent-onset psychoses as visualized by positron electron tomography [14,34]. In an activated state, microglia cells can

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http://dx.doi.org/10.1016/j.bbacli.2015.06.007

produce free radicals, pro-inflammatory components and other neurotoxic substances, causing cell death in their proximity [27], while at rest microglia are an important source of growth factors. The activation of microglia cells provides a possible route by which an increased pro-inflammatory state in the brain could cause increased grey matter loss and more severe negative and cognitive symptoms.

In support of this line of thought, cross-sectional studies showed a negative correlation between an inflammatory parameter in the blood (C-reactive protein; CRP) and cognitive performance in people with schizophrenia [12,13]. CRP and other inflammatory markers (including S100B, interleukin [IL]-6 and IL-8) have also been associated with severity of negative symptoms [26]. Furthermore, MRI studies showed larger cerebral volume decreases in poor outcome patients, characterized by more symptoms and lower levels of daily life functioning [35,36]. This more pronounced brain volume loss occurs mainly in the first years of illness [4,8] and may be related to increased inflammatory status in the brain. A recent meta-analysis [38] including 26 double-blind randomized controlled trials evaluated the efficacy of anti-inflammatory agents, showing promising results. Aspirin addition was found to have beneficial effects (mean weighted effect size [ES]: 0.3, $n = 270$), as well as estrogens (ES: 0.51, $n = 262$), and N-acetylcysteine (ES: 0.45, $n = 140$).

This mounting body of evidence suggests that anti-inflammatory drugs can be viewed as potential candidates for new augmentation therapies, although at this stage it is unknown if increased pro-inflammatory status is characteristic for all patients with schizophrenia or just for a specific subset of them. A recent post-mortem study showed clear signs of increased inflammation in some 40% of patients [15], which parallels findings in peripheral blood also showing increased inflammation in 35% of patients [29]. Thus, augmentation with an anti-inflammatory component may be particularly beneficial for this subgroup.

Sierra et al. [30] compared nine statins for their potential as a neuroprotective agent and concluded that simvastatin is the best candidate for the prevention of neurodegenerative conditions due to its high capacity to penetrate the blood–brain-barrier, strong cholesterol lowering effect on neurons and (in vitro) protection against neural cell death. However, statins have anti-inflammatory effects that are independent of their ability to lower cholesterol. Individuals with schizophrenia already have high levels of cardiovascular risk factors [18]. Statin treatment that combines anti-inflammatory with cardioprotective properties may therefore have particular potential as adjuvant therapy in patients with recent-onset schizophrenia.

1.1. Aims

We hypothesize that simvastatin addition will have a beneficial effect in patients with early-stage psychotic disorder on the following outcome variables:

- Primary: Symptom severity and cognitive performance;
- Secondary: Brain volume loss, global functioning, movement disorders, and metabolic and inflammatory parameters.

2. Methods

2.1. Overview

This is a randomized, double-blind, placebo-controlled study of simvastatin addition 40 mg/day for patients with recent-onset psychosis. A placebo-controlled design was chosen in order to differentiate between clinical effects of simvastatin and effects associated with experimental treatment, such as induced expectations of participants. Randomization is applied to minimize bias. A total of 250 patients with a DSM-IV diagnosis of schizophrenia, schizoaffective or schizophreniform disorder, or psychotic disorder NOS (not otherwise specified) will be included in a period of three years, between 18 and 50 years of age and onset of first psychosis no longer than three years ago. Multiple psychosis-related diagnoses are allowed within this study, as recent scientific developments substantiate that these diagnoses share an underlying pathophysiology. This scientific development is illustrated by the editorial comment by NIMH director Thomas Insel (http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml).

Patients will be recruited from both inpatient and outpatient settings throughout the Netherlands. The patients will be identified and first approached by their treating psychiatrist and the multidisciplinary teams. When patients are eligible to participate after the screening procedure, they will be randomized to simvastatin or placebo. Clinical and cognitive assessment will be done during the baseline visit, in addition to an MRI scan, after which the patient will start with the study medication. Patients will continue with their antipsychotic medication as usual during the trial. Study assessments will be conducted by members of the study team, while the treating psychiatrist will remain in charge of the overall treatment. Any changes in type or dosage of antipsychotic medication will be recorded on each study visit. During the course of the study the patient will also have additional support from the study team and continued support from their mental health care team.

2.2. Allocation

All 250 patients will be randomized 1:1 to either 40 mg simvastatin or placebo daily, with a treatment period of 12 months while continuing their antipsychotic medication as prescribed by their treating physician. A web-based application will be used, and stratification will be applied for center and gender. Trial treatment randomization codes will not be available to the study staff, but will be conveyed to the pharmacy in the University Medical Centre Utrecht in case emergency deblinding is needed. Emergency unblinding is only allowed in case of serious concerns about patient safety.

2.3. Inclusion criteria

1. A DSM-IV-R diagnosis of: 295.x (schizophrenia, schizophreniform disorder, or schizoaffective disorder) or 298.9 (psychosis NOS)
2. Onset of first psychosis no longer than 3 years ago
3. Age between 18 and 50 years
4. Written informed consent is obtained.
5. Female patients of childbearing potential need to utilize a proper method of contraception.

2.4. Exclusion criteria

1. Fulfillment 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);
2. Presence of any of the contra-indications or warnings for the use of simvastatin as reported in the SPC;
3. Chronic use of glucocorticosteroids (temporary use is permitted, if stopped at least 1 month before start of treatment trial);
4. Chronic use of non-steroidal anti-inflammatory drugs (temporary use is permitted, if stopped at least 1 month before start of treatment trial);
5. Current use of statins or other lipid-lowering drugs;
6. Pregnancy or breast-feeding (urine pregnancy test will be performed for sexually active females with child bearing potential);
7. 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 aminotransferase (ASAT), alanine aminotransferase