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A randomized placebo-controlled pilot study of pravastatin as an adjunctive therapy in schizophrenia patients: Effect on inflammation, psychopathology, cognition and lipid metabolism

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ABSTRACT

Objective: The aim of this study was to investigate the role of pravastatin, as an adjunctive therapy, on inflammatory markers, lipid and glucose metabolism, psychopathology, and cognition in subjects with schizophrenia and schizoaffective disorder.

Methods: Schizophrenia or schizoaffective subjects (N = 60) were randomized to receive either a 12-week supply of pravastatin 40 mg/day or placebo treatment. Anthropometric measures, lipids and glucose metabolism, inflammatory markers, psychopathology and cognitive performance were assessed at baseline, 6 weeks and 12 weeks.

Results: Pravastatin use was associated with a significant decrease in total cholesterol, low density lipoprotein (LDL) cholesterol and LDL particle number levels, but was not associated with any significant changes in cognition or psychopathology in the participants, except a significant decrease in the Positive and Negative Syndrome Scale (PANSS) positive symptom score from baseline to week 6. However, this decrease failed to remain significant at 12 weeks. Interestingly, triglycerides, LDL-cholesterol, total cholesterol, LDL particle number, small LDL particle number, large very low density lipoprotein (VLDL) particle number and C-reactive protein (CRP) followed a similar pattern at 6 and 12 weeks as psychopathology.

Conclusions: These results suggest that a randomized trial with a larger sample size and a higher dosage of pravastatin would be helpful in further evaluating the anti-inflammatory properties of pravastatin, its association with improvements in cognitive symptoms, and its potential to reduce positive and negative symptoms associated with schizophrenia or schizoaffective disorders.

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1. Introduction

Immune dysfunction and inflammation have been described in patients with schizophrenia (Miller et al., 2014; Najjar and Pearlman, 2014). Prenatal infections and maternal immune alterations have been implicated as significantly increasing the risk of schizophrenia in offspring and schizophrenia-related neurocognitive/neuroanatomical abnormalities (Brown et al., 2004; Gilmore et al., 2004; Meyer et al., 2009; Miller et al., 2013). Neuroinflammation can injure developing oligodendroglia, resulting in prominent white matter pathology and motor, cognitive, and behavioral impairment which are all associated with pre-psychosis and schizophrenia (Chew et al., 2013; Najjar and Pearlman, 2014). Elevated levels of cytokines have been described not only in schizophrenia patients but also in acutely relapsed patient with schizophrenia (Miller et al., 2011) and in unaffected first degree relatives of patients with schizophrenia (Martinez-Gras et al., 2012). Previous research has also suggested a relationship between inflammation and acute coronary syndromes as well as metabolic syndrome (Maury and Brichard, 2010; Libby et al., 2014).

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Pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 are soluble polypeptide signaling proteins that play crucial roles in the early defense against infection and the initiation and/or progression of inflammation (Meyer et al., 2009). Cytokines, particularly interleukin-6 (IL-6), are the primary inducers of acute phase proteins, including C-reactive protein (CRP) which is an acute phase protein produced by hepatocytes whose serum concentration increases under acute and chronic inflammatory conditions (Black et al., 2004; Agrawal, 2005; Miller et al., 2014).

In the past decade, it has been clearly established that obesity, insulin resistance and type 2 diabetes are closely associated with chronic inflammation characterized by abnormal cytokine production; increased acute-phase reactants and other mediators; and activation of a network of inflammatory signaling pathways (Wellen and Hotamisligil, 2005; Miller et al., 2011).

Several studies have suggested that inflammatory and immunological processes are likely related to the manifestation of symptoms and treatment response of schizophrenia (McAllister et al., 1995; Zhang et al., 2004). Our group has reported that elevated levels of CRP are associated with marked negative symptoms and higher Positive and Negative Syndrome Scale (PANSS) scores in patients with schizophrenia (Fan et al., 2007). In a multi-center, cross-sectional study with a sample of 199 schizophrenia outpatients, we found that elevated white blood cell (WBC) counts are associated with worse clinical symptoms of schizophrenia as measured by the Brief Psychiatric Rating Scale (BPRS) total scores after controlling for potential confounding variables (Fan et al., 2010).

Inflammation is also associated with impaired cognition in schizophrenia. In a sample of 413 patients with schizophrenia, Dickerson et al. reported that those with CRP ≥ 5 mg/mL had significantly lower cognitive scores than those with CRP < 5 mg/mL (Dickerson et al., 2007).

Some recent experimental studies have shown that besides their effects on the primary and secondary prevention of cardiovascular diseases, statins may also have beneficial anti-inflammatory effects through diverse mechanisms that have been recognized from in vivo and in vitro studies in experimental models (Forero-Pena and Gutierrez, 2013). Statins reduce atherogenesis and concomitantly the inflammatory state as reflected by the decreased serum levels of CRP. The mechanism by which statins lower CRP levels is still unknown (Ridker et al., 2005a, 2008; Pearson et al., 2009).

Growing evidence from clinical studies with COX-2 inhibitors shows that anti-inflammatory drugs may have beneficial effects in schizophrenia, in particular in an early stage of the disorder (Muller et al., 2012). Drugs that possess anti-inflammatory effect might improve both psychiatric symptoms and metabolic disturbances in patients with schizophrenia.

Given the need for additional treatments, the present study was designed to determine if such a treatment warrants further investigation. We chose to use pravastatin, one of the most extensively studied statins in both primary and secondary prevention trials (del Sol and Nanayakkara, 2008), available in generic form, because it appears to have fewer side effects than other statins such as simvastatin (Kaesemeyer et al., 1999; Ridker et al., 2005a, 2005b). Additionally, some research suggests that pravastatin can significantly lower CRP levels and IL-6 concentration, as well as significantly improve insulin resistance (Ridker et al., 1999; Güçlü et al., 2004; Asanuma et al., 2008).

We conducted a 12-week, randomized, double-blind, placebo-controlled pilot study of pravastatin 40 mg/day, as an adjunctive therapy in 60 schizophrenia subjects to examine pravastatin's effects on inflammatory markers, lipid and glucose metabolism, psychopathology, cognition, and positive and negative syndrome scale (PANSS).

2. Methods

Subjects were recruited from the Freedom Trail Clinic at the Erich Lindemann Mental Health Center and procedures were performed at the Mallinckrodt General Clinical Research Center at the Massachusetts General Hospital (MGH), Boston. The study was approved by the institutional review boards of MGH and the Massachusetts Department of Mental Health. A total of 81 male and female outpatients between the ages of 18 and 68 years with the diagnosis of schizophrenia, any subtype, or schizoaffective disorder, any subtype, were screened for the study and 60 were randomized. After providing written informed consent, subjects underwent a diagnostic evaluation by a research psychiatrist using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID).

Subjects who were treated and compliant with their outpatient medications (any antipsychotic) were eligible for participation. Subjects were excluded on the basis of inability to provide informed consent, participation in other research studies, unstable psychiatric illness, current alcohol or substance abuse, current treatment with insulin, pregnancy, untreated thyroid disease, significant medical illness including severe cardiovascular, hepatic, or renal disease (serum creatinine > 1.5 mg/dL), anemia (hemoglobin < 11.0 mg/dL), history of severe head injury, or untreated muscle disease. Subjects treated with the following medications known to affect glucose tolerance were also excluded: anti-inflammatory drugs (including aspirin and ibuprofen), thiazide diuretics, agents that induce weight loss, or St John's Wort. Similarly, subjects treated with colchicine, azole antifungals, macrolide antibiotics, HIV protease inhibitors, or a known hypersensitivity to pravastatin or to any of its components were excluded from the study. Baseline results of subjects with low density lipoprotein (LDL) cholesterol >160 mg/dL with no co-morbidities, LDL >130 mg/dL for people with risk factors for cardiovascular disease, and LDL > 100 mg/dL for people with diabetes mellitus were sent to the subjects' primary care physician with their written consent. Subjects who did not receive lipid lowering medication treatment within 6 weeks following the referral to the PCP were reassessed to determine eligibility for randomization. Study subjects who were eligible for randomization received a 12-week supply of pravastatin (40 mg/day) or placebo.

2.1. Baseline evaluation

Baseline medical evaluation included weight, height, waist circumference, and vital signs with sitting and standing blood pressure, Abnormal Involuntary Movement Scale (AIMS), a physical examination and a nutritional assessment (including the evaluation of a food record, indirect calorimetry, and anthropometric measures). A 12-lead EKG was obtained and analyzed by the Department of Cardiology at the Massachusetts General Hospital.

Blood samples were obtained for fasting glucose and insulin levels, comprehensive metabolic assessment (kidney and liver function, electrolytes and acid/base disorders), lipid profile, complete blood count with differential, LDL particle size, CRP, IL-6, TNF-α, glycohemoglobin (HbA1c), and creatine kinase (CK). A urine drug screen and a urine pregnancy test were performed to determine if subjects met eligibility criteria.

2.2. Laboratory assays

Laboratory assays were performed by the Chemistry Lab at the MGH and LabCorp. Serum insulin assays were performed using an Immulite Analyzer (Diagnostic Product Corporation, Los Angeles, CA) with an intra-assay coefficient of variation of 4.2–7.6%. Fasting plasma glucose was measured with a hexokinase reagent kit (A-gent glucose test, Abbott, South Pasadena, California). Glucose assays were run in duplicate, and the intra-assay coefficient of variation ranged from 2% to 3%. The plasma concentrations of IL-6 were measured by a commercially available enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn). Serum levels of CRP were measured via a high-sensitivity latex-enhanced immunonephelometric assay on a BN II

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