Lovastatin for the adjunctive treatment of schizophrenia: A preliminary randomized double-blind placebo-controlled trial ☆

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ABSTRACT

While statins target many of the pathways to neuroprogression in schizophrenia, the safety and efficacy of statins for treating schizophrenia has never been examined. This is an 8-week randomized double blind controlled clinical trial examining the efficacy and safety of adjunctive lovastatin (20 mg/day) treatment or placebo for people with schizophrenia. The baseline characteristics of the two groups were not different. Endpoint changes in Positive and Negative Syndrome Scale (PANSS) total and subscale scores did not differ between the two groups. However there was a significant difference between the doses of risperidone used in the two groups. The mean dose in the lovastatin and placebo groups were 4.8(1.8) and 3.4(1.4) mg/day, respectively ($P < .03$). No serious adverse events were reported. Slowness of movements, muscle rigidity, increased appetite, and decreased energy were the most common adverse effects, and these rates did not differ between the two groups. This study failed to demonstrate a benefit of lovastatin on symptoms of schizophrenia. This combination was well tolerated. However, a higher dosage of risperidone was used for treating the disorder in those taking concomitant lovastatin compared to placebo.

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1. Introduction

Schizophrenia is a disorder of unknown etiology. Inflammation is one possible etiological pathway with studies investigating the role of a number of cytokines including interleukin 1(IL-1) and interleukin 6 (IL-6) in patients with schizophrenia (Berk et al., 2008b; Song et al., 2009). In people with schizophrenia, serum levels of interleukin-1beta (IL-1beta) (Chang et al., 2011; Soderlund et al., 2009; Song et al., 2009) and tumor necrosis factor-alpha (TNF-alpha) are higher than that of those healthy subjects (Song et al., 2009). IL-1 activates

and increases nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB), whose activity is also increased in schizophrenia (Song et al., 2009). However, the data regarding increased levels of IL-6 are inconsistent (Singh et al., 2009). A meta-analysis of cytokines in schizophrenia suggests that interleukin-1β, interleukin-6, and transforming growth factor-β may markers of acute illness exacerbations, while interleukin-12, interferon-γ, tumor necrosis factor-α, and soluble IL-2 receptor may be trait markers of the disorder (Miller et al., 2011). Antipsychotics have effects on cytokines, with a recent meta-analysis showing reduction in pro-inflammatory cytokines such as interleukin-1β and interferon-γ, and reduction in plasma levels of soluble interleukin-2 receptor (Tourjman et al., 2013). Germane to this study, risperidone decreases serum levels and mRNA expression of IL-1beta in people with schizophrenia (Song et al., 2009).

There is an increased risk of schizophrenia in children of the mothers who experience infection in pregnancy. A single maternal injection of IL-6 to a pregnant mouse causes expression of a model of schizophrenia in adult offspring, while IL-6 knock-out mice do

not show these features (Smith et al., 2007). Pro-inflammatory cytokines such as IL-1beta induce lethargy, anhedonia, social withdrawal, and cognitive problems that are analogous to the negative symptoms and cognitive problems in schizophrenia and depression (Dantzer and Kelley, 2007). IL-1beta also causes dopaminergic and glutamatergic abnormalities akin to those reported in schizophrenia (Soderlund et al., 2009). Anti-inflammatory effects of IL-6 is mediated through inhibition of TNF-a and IL-1, and activation of IL-1ra and IL-10 (Donev and Thome, 2010).

These findings led researchers in schizophrenia to conduct studies to examine if reducing inflammation might be of clinical benefit. Add-on treatment with celecoxib plus risperidone was superior to risperidone alone in decreasing positive symptoms of schizophrenia (Akhondzadeh et al., 2007; Muller et al., 2002). Celecoxib inhibits activity of cyclooxygenase-2 (COX-2), a mediator of inflammation in the brain. Cytokines such as Il-6, IL-10, and Il-2 activate this enzyme. As levels of IL-6 (Akiyama, 1999; Kim et al., 2009) and IL-10 are high in schizophrenia, celecoxib down-regulates COX-2 activity leading to the reduction of inflammation. In a similar manner, aspirin which is the original anti-inflammatory agent (Berk et al., 2013), improved the core features of schizophrenia (Laan et al., 2010). A recent meta-analysis of anti-inflammatory treatment of schizophrenia documented the poten-tial utility of COX-2 inhibitors and minocycline in schizophrenia (Fond et al., 2014).

Statins are widely used and effective lipid lowering agents. They inhibit 3-hydroxy-3-methylglutaryl-CoA reductase. However, statins have other effects which are cholesterol independent such as decreasing oxidative stress and inflammation. Recently, it has been shown that statins inhibit brain inflammation. Simvastatin inhibits inflammation by the reduction of IL-1beta and TNF- alpha (Hernandez-Romero et al., 2008). It also increases BDNF expres-sion which has neuroprotective effects (Hernandez-Romero et al., 2008). Atorvastatin decreases IL-βand TNF- αexpression as well as the production of IL-1β, IL-6 and TNF-α in the hippocampus (Zhang et al., 2013). Atorvastatin is thus a potential neuroprotec-tive agent (Castro et al., 2013). Lovastatin significantly decreases mRNA expression of IL-1beta, IL-6, TNF- alpha, and kinin B1 receptor in animals (Chen et al., 2007; Gouveia et al., 2014). There are data that they may have psychotropic effects especially in depression (Ghanizadeh and Hedayati, 2013; O'Neil et al., 2012). However, lovastatin neither decreases no increases mania symp-toms in patients with bipolar mood disorder (Ghanizadeh et al., 2014). A recent meta-analysis reported that statin use may be associated with a lower risk for the development of depression (Parsaik et al., 2014). However, a retrospective, observational, population-based study did not show any association between statin use and the risk of development psychological disorders (Mansi et al., 2013).

Moreover, dyslipidaemia in people with schizophrenia is very common. Some psychotropic agents, particularly atypical antipsycho-tics, increase lipid levels (Wirshing et al., 2002). Furthermore, a sedentary lifestyle is common in schizophrenia, increasing the risk of cardiovascular problems. Lipid lowering medications reduce cardi-ovascular risk by decreasing triglycerides and cholesterol (Expert Panel on Detection, E., Treatment of High Blood Cholesterol in, 2001). Rosuvastatin decreased dyslipidemia in patients with schizophrenia treated with antipsychotics (De Hert et al., 2006). A study reported absence of pharmacological interactions between clozapine and lovastatin and atorvastatin and pravastatin (Landry et al., 2008). A retrospective study showed that statins decreased total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) (Vincenzi et al., 2013). Statins may consequently be considered as a potential primary preventive and treatment approach in schizophrenia. Nevertheless, the efficacy and safety of statin use in psychotic disorders in terms of psychiatric endpoints has not been investigated (Mascitelli et al., 2008).

Concordant with the above mentioned evidence, it was not a primary hypothesis that lovastatin, on the basis of its anti-inflammatory effects, may decrease symptoms of schizophrenia using the PANSS but as a post-hoc finding.

2. Methods

2.1. Participants

This is a randomized double-blind placebo-controlled add-on trial in patients with schizophrenia. The clinical sample consisted of 36 inpatients with schizo-phrenia in the active phase of this disorder diagnosed according to DSM-IV diagnostic criteria. They were randomized in a 1:1 ratio to lovastatin (20 mg/day) or placebo. The starting dose of lovastatin was 10 mg/day titrated up 20 mg/day after one week. The duration of study was 60 days. All participants both groups were concurrently administered risperidone (2 to 8 mg/day).

Inclusion criteria were: a diagnosis of schizophrenia using DSM-V diagnostic criteria, written informed consent provided by the patient and/or caregiver, aged between 18 and 66 years of age, not currently taking a statin medication, no evidence of active substance abuse or dependence and a PANSS baseline total score of ≥ 50. Use of concomitant non-investigational medications such as biperidin was permitted.

Exclusion criteria were: use of long acting antipsychotics in the last 2 months prior to this study, serious medical or neurological illness such as seizures, hypothyroidism, diabetes, encephalitis, liver disease, cancer, unstable heart failure, uncontrolled hypertension/asthma/COPD; psychotic disorder due to a general medical condition or substance use, use of medications with significant interactions with lovastatin, pregnant women or the patients planning to be pregnant during this study, or women not using adequate birth control methods, lactation, currently taking a statin or any of the following: anti-inflammatory drugs or aspirin; systemic antibiotics, anti-viral or anti-fungal drugs (within the past 4 weeks); potent inhibitors of the cytochrome P450 isoform 3A4 (CYP3A4) including digoxin, nefazodone, cyclosporine, warfarin, amiodarone or verapamil.

The mean dose of risperidone required for treating patients with schizophrenia was at clinician discretion. The Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987) was used to evaluate the clinical symptoms of schizophrenia. Treatment emergent adverse effects were evaluated using a checklist.

Considering a difference of four points on the PANSS total score between the lovastatin and placebo groups, a standard deviation (SD) of four, a two-tailed $P < 0.05$, and a power of 80%, a sample size of 34 was calculated.

2.2. Statistical analysis

Data analysis was performed using SPSS for windows. Intention-to-treat analysis (ITT), using last observation carry-forward (LOCF) method, was used to impute missing data related to any participants who dropped out this trial. Mann–Whitney tests were performed to compare age, body mass index, PANSS total score, PANSS negative total score, PANSS positive total score, and PANSS general psychopathology total score between the two groups. Chi-squared tests were used to compare the gender ratio, marital status, and subtype of schizophrenia between the two groups. Fisher's exact test was used to compare categorical variables between the two groups whenever applic-able. P values less than 0.05 were considered significant.

3. Results

Three screened patients did not provide informed consent, and were not entered this trial. There were 20 patients in the lovastatin group and 16 patients in the placebo group. Six participants (four in the lovastatin group and two in the placebo group) dropped out after the third assessment. Medication adherence of six participants was poor, and they were excluded. No participants dropped out due to treatment emergent adverse effects. A consort flow chart is shown in Fig. 1.

The mean age (SD) of the patients in the lovastatin and placebo groups was 30.8(8.9) and 30.1(6.5) years, respectively ($P=0.7$). The mean years of education, smoking rates, marital status, schizo-phrenia subtype, baseline total PANSS score, baseline PANSS positive score, baseline PANSS negative score, baseline PANSS general psychopathology score and body mass index (BMI) did not differ between the groups (Table 1).