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Inflammation and treatment response to sertraline in patients with coronary heart disease and comorbid major depression ☆

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ABSTRACT

Objective: Treatment-resistant depression has recently emerged as a marker of increased risk for morbidity and mortality in patients with coronary heart disease (CHD). Studies in depressed patients without CHD suggest that elevated markers of inflammation predict poor response to treatment. This may help to explain the increased risk of cardiac events associated with depression. We therefore studied the relationship between pretreatment markers of inflammation and treatment response in patients with CHD and major depression.

Methods: This was a planned, secondary analysis of a clinical trial in which 122 patients with CHD and comorbid major depression were randomly assigned to 50 mg of sertraline plus 2 g/day omega-3 fatty acids or to 50 mg of sertraline plus 2 g/day corn oil placebo capsules for ten weeks. Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II). Blood samples were collected at baseline to determine levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α). The primary outcome was the post-treatment BDI-II depression score.

Results: Baseline levels of hs-CRP, IL-6, and TNF-α were not associated with the 10-week post-treatment depression score (P=.89, P=.88, and P=.31, respectively). Treatment responders (>50% reduction from baseline BDI-II score) did not differ from non-responders in either baseline hs-CRP, IL-6, or TNF-α (P=.83, P=.93, and P=.24, respectively). Similarly, depression remitters (BDI-II ≤8 at post-treatment) did not differ from non-remitters on the three baseline inflammation markers.

Conclusion: These findings do not support the hypothesis that elevated baseline inflammatory markers predict poor response to sertraline in patients with CHD and major depression. The explanation for the increased risk of cardiac events associated with poor response to depression treatment remains unclear.

Introduction

Depression is a risk factor for cardiovascular morbidity and mortality in patients with coronary heart disease (CHD) [1,2]. There has been growing interest in identifying the depression subtypes that carry the highest risk. Some evidence exists that patients with a first episode of depression and those whose depression began following a cardiac event, may be at especially high risk [3,4]. In addition, there is evidence that depression that does not respond to standard treatment may be a high-risk form of depression. Approximately 20–30% of depressed patients fail to respond even to multiple antidepressant treatments [5]. Secondary analyses of several randomized, controlled trials in patients with CHD showed that those who do not respond to depression treatment may be at a particularly high risk for mortality [5]. The explanation for this risk is unknown.

Inflammatory processes have been associated with the progression of coronary artery disease and with cardiac events, including myocardial infarction [6]. A recent meta-analysis found that increased levels of the inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6), are associated with depression, both with and without comorbid CHD [7]. Another meta-analysis showed that tumor necrosis factor alpha (TNF-α) was also increased in major depression [8].

In depressed patients without heart disease, high baseline levels of inflammatory markers have been associated with poor treatment response [9,10], although not all studies have found this [11]. In a study of patients with a recent acute coronary syndrome (ACS), those with persistent depression showed a trend towards higher baseline and follow-up CRP levels compared to remitted depressed patients [12].

☆ Trial Registration: NCT00116857, www.clinicaltrials.gov.

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No studies have examined the relationship between pre-treatment inflammation and treatment response in stable CHD patients with major depression. It is possible that elevated levels of inflammatory molecules may explain the increased risk of cardiac events in patients who do not respond well to antidepressant treatment.

The purpose of this study was to determine whether pretreatment levels of high-sensitivity CRP (hs-CRP), IL-6, and TNF-α predict response to treatment with 50 mg/day of sertraline in patients with CHD and comorbid major depression. We hypothesized that high levels of inflammatory markers are associated with poor response to depression treatment.

Methods

Participants and study design

This study was a planned, secondary analysis of data from a randomized, double-blind, placebo-controlled trial to determine whether omega-3 augmentation improves the efficacy of sertraline for the treatment of major depression in persons with CHD [13]. The study data provided no evidence that omega-3 augmentation increases the efficacy of sertraline for depression in patients with CHD [13]. The methods and results of the trial have been described previously [13].

Briefly, patients were recruited for this study between May, 2005 and December, 2008 from cardiology practices in St. Louis, MO, USA, and from cardiac diagnostic laboratories affiliated with Washington University School of Medicine. Patients were eligible to participate if they had documented CHD, met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for a current major depressive episode, had a Beck Depression Inventory-II (BDI-II) score of ≥16, and still had a diagnosis of major depression following the two week pre-randomization phase of the study.

CHD was documented by ≥50% stenosis in ≥1 major coronary artery, a history of coronary revascularization, or hospitalization for an ACS at least 2 months prior to enrollment. Exclusion criteria were (1) cognitive impairment, comorbid major psychiatric disorders, psychosis, a high risk of suicide, or current substance abuse; (2) ACS or revascularization within the previous two months, a left ventricular ejection fraction <30%, a diagnosis of heart failure, advanced malignancy, or a physical impairment that would prevent participation; (3) ongoing use of an antidepressant, anticonvulsant, lithium, or omega-3 supplement; (4) sensitivity to sertraline or omega-3; and (5) physician or patient refusal. All participants gave written informed consent. The study was approved by the Human Research Protection Office at Washington University.

Intervention

The participants were randomly assigned to the omega-3 or the placebo arm by a permuted block random allocation program (SAS Institute, Cary, NC, USA). All participants were prescribed 50 mg/day of sertraline for 10 weeks. In addition to sertraline, the omega-3 group received 2 g/day omega-3 acid ethyl esters, containing 930 mg eicosapentaenoic acid and 750 mg docosahexaenoic acid. The placebo group received sertraline plus 2 g/day placebo corn oil. The omega-3 fatty acids and corn oil were provided in two capsules each day for 10 weeks. The participants, research nurses, and investigators were blinded to treatment assignment during the trial. In order to assess medication adherence, participants were asked to return any unused pills and to confirm that the pills that were not returned had been taken as prescribed.

Measurements

Depression

The 21-item BDI-II was administered weekly for 10 weeks, starting at baseline, to monitor changes in the severity of depression [14]. At baseline and at a 10-week post-treatment evaluation, interviewer-rated depression severity was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D) [15]. On both scales, higher scores reflect more severe depressive symptoms. Both instruments are widely used for assessing depression outcomes in clinical trials, and have established reliability and validity [14,15]. We defined treatment responders as participants who had a >50% reduction on the BDI-II from baseline. Patients with a post-treatment BDI-II score ≤8 were classified as depression remitters. The primary study outcome was the post-treatment BDI-II score. Secondary outcomes include the post-treatment HAM-D score, and the response and remission rates based on the BDI-II.

Inflammation

Oral body temperature was measured at baseline in order to exclude patients with infectious diseases or other disorders that could cause a systemic increase in inflammatory markers. Blood samples were drawn at baseline and after 10 weeks of treatment to determine hs-CRP, IL-6, and TNF-α levels. Patients were asked to refrain from taking antihistamines, anti-platelet agents, and nonsteroidal anti-inflammatory agents including aspirin for 24 h prior to the blood draws. The specimens were spun and frozen immediately.

hs-CRP was determined by an enhanced immunonephelometric assay on a BN II analyzer (Dade Behring; Newark, NJ, USA). This assay can measure hs-CRP levels of less than 1 mg/dl with assay coefficients of variation below 10%. IL-6 and TNF-α were measured by high-sensitivity enzyme-linked immunosorbent assay (Quantikine HS, R&D Systems) according to the manufacturer's specifications.

Statistical analyses

Because of the possibility that omega-3 fatty acids might have affected the relationship between inflammation and depression outcome, we tested for interactions between treatment allocation and inflammatory markers in all analyses. If the interaction term was significant, the analysis was stratified by treatment group, otherwise, the analysis was conducted without stratification. A linear regression model was used to examine the relationship between baseline inflammation and post-treatment depression scores, adjusting for baseline depression scores and treatment allocation. Sensitivity analyses were conducted to determine whether the addition of age, sex, smoking status, aspirin and statins altered the association between baseline inflammation and depression outcome. Analysis of variance was used to compare the baseline levels of inflammatory markers of the responders vs. nonresponders and remitters vs. nonremitters. hs-CRP, IL-6, and TNF-α distributions were found to be positively skewed, and therefore, natural logarithm-transformed values were analyzed for these variables. The Pearson correlation between change in inflammation from baseline to posttreatment and change in depression score from baseline to post-treatment was also calculated. The distributions of the changes in inflammatory levels were approximately normal. Hence, these raw values were analyzed without transformation. The two-tailed alpha level for significance was set at .05. SAS version 9.1 was used for all statistical analyses.

Results

One hundred twenty-two patients (41 women, 34%) participated in the study. The mean age was 58±9 years. All participants had body temperatures within the normal range on the day of the blood draw. Adherence to sertraline was >98%. Table 2 displays the pre- and post-treatment depression scores and levels of inflammatory markers. Seven participants did not complete the study. Reasons for discontinuation of participation were: withdrawal to try another antidepressant (n=2), refusal (n=2), insomnia, or dizziness (n=2), and hospitalization because of worsening of a pre-existing medical condition (n=1). One hundred fifteen participants completed the study. Of these, baseline hs-CRP, IL-6, and TNF-α levels were measured in 106, 113, and 112 participants, respectively. Patients with missing baseline inflammatory markers or