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CORRESPONDENCE

Sertraline treatment decreased the serum levels of interleukin-6 and high-sensitivity C-reactive protein in hematopoietic stem cell transplantation patients with depression; a randomized double-blind, placebo-controlled clinical trial

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Psychological disorders (e.g., depression and anxiety) are associated with post-HSCT complications through affecting the inflammation process [1]. The elevated pro-inflammatory cytokines in depressed adults compared with healthy individuals and the effect of selective serotonin reuptake inhibitors (SSRIs) in reduction of TNF-α, IL-6, and IL-12 and increase of IL-4 and IL-10 in both healthy individuals [2], and patients with major depression in different clinical settings indicate the reciprocal relationship between inflammation and depression [3, 4]. The aim of the present clinical trial is to investigate the probable effects of sertraline, a proven effective SSRI with favorable safety, and drug interaction profile on IL-6, IL-10, and hs-CRP in depressed HSCT recipients.

A simple randomized, double-blind, placebo-controlled clinical trial, registered in Iranian Registry of Clinical Trials (IRCT 201310083210N4), was performed in the Taleghani Hospital, Tehran, Iran. The study received Hospital Ethics Committee approval and all patients were given informed consent forms. Sample size calculation was based on $\alpha = 0.05$, 80% power ($1\text{-}\beta = 0.8$) and 20% possible losses to follow-up.

The hospital anxiety and depression scale (HADS) questionnaire was used to assess the patients' depression, based on self-reports at the baseline, 2, 4, and 8 weeks of treatments. The cutoff score ≥8 out of total possible 21 was assumed to define depressed patients and >50% reduction from baseline score was considered as response to treatment.

The immunochemiluminescence assay was used for mesurement of serum hs-CRP (Immulite, DPC, USA) and the enzyme-linked immunosorbent assay (ELISA) was used for the determination of IL-6 (Amersham Bioscience, USA) and IL-10 (Bender MedSystems, Austria) levels in serum samples of patients taken at the baseline, 4 and 8 weeks.

Experiments were performed triplicate and data were analyzed using two-tailed tests by SPSS 20. Normality of variables was checked by the Kolmogorov–Smirnov test. *t*-test or Mann–Whitney U test, Chi-square, or Fisher exact test, one-way ANOVA repeated measurement or Friedman's test were used for data analysis. *P*-values <0.05 were considered as significant.

There were no significant differences found between sertraline and placebo groups, regarding demographic and clinical variables, conditioning regimen, received medications and the frequency of adverse effects during the study (Table S1).

Supplementary information The online version of this article (https://doi.org/10.1038/s41409-019-0623-0) contains supplementary material, which is available to authorized users.

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Table 1 Serum levels of IL-6, IL-10, and hs-CRP

	Groups		*P*-value
	Sertraline ($n = 24$)	Placebo ($n = 20$)	
IL-6 serum level (pg/mL)			
Baseline	104 (66)	103 (208)	0.608
Week 4	61.10 (30)	93.50 (214)	0.061
Week 8	42.45 (46.8)	82.25 (55)	**0.001**
Baseline to week 4	−38.20 (46)	−25.35 (161)	0.283
Baseline to week 8	−64 (60)	−22 (89)	**0.048**
IL-10 serum level (pg/mL)			
Baseline	81 (25)	114 (176)	0.079
Week 4	66 (68.65)	94 (96.2)	0.110
Week 8	77.10 (25.35)	109 (79.25)	0.079
Baseline to week 4	−23.70 (37.2)	−9.65 (183)	0.537
Baseline to week 8	−10.45 (54)	−33.05 (145.5)	0.458
hs-CRP serum level (mg/L)			
Baseline	3 (3.5)	5.5 (10)	0.153
Week 4	66 (36)	55 (11)	0.484
Week 8	3.15 (4.63)	9 (13.85)	**0.031**
Baseline to week 4	55 (43)	50 (38)	0.635
Baseline to week 8	−0.9 (5.6)	1.45 (11.7)	0.147

The results of the comparison of data between two groups were shown as *P*-value, of which the bold ones are statistically significant. Values represent as median (IQR)

Pg picogram, *mL* milliliter, *mg* milligram, *L* liter

Sertraline and placebo significantly alleviated HADS scores in 15 (62.5%), and 2 (10%) patients, respectively. This difference was significant ($P < 0.001$). At the end of the study, HADS scores were significantly lower ($P = 0.001$) and changes from baseline to the 4 and 8 weeks of the study were greater in the sertraline vs. placebo group ($P < 0.001$ for both time intervals [Table S1]).

Compared with baseline, median levels of IL-6 significantly decreased in a significant manner at week 8 of treatment in the sertraline group. Median levels of IL-6 were significantly lower at the end of the study and changes in the IL-6 level from baseline to week 8 were significantly greater in the sertraline vs. placebo group ($P = 0.001$ and 0.048, respectively). IL-10 displayed no significant differences neither in inter-, nor in intra-group comparisons during the study. Except for the significant difference of hs-CRP between sertraline and placebo at week 8 ($P = 0.031$); its changes from baseline did not differ significantly between two groups (Table 1).

Bidirectional and interdependent relationship between depression and inflammation is reported in studies. Depression can result in upregulation of inflammatory mediators and pathways and inflammation can contribute to depressive symptoms [5]. In HSCT setting, it was reported recently that depression significantly associated with higher levels of serum IL-6, and the IL-6-to-IL-10 ratio [6].

Our finding of decreasing effect of sertraline on the serum levels of IL-6 and hs-CRP in HSCT patients after 8 weeks of treatment compared with placebo is in agreement with studies in depressed healthy and patient subjects [3, 7]. However, there are discrepancies in findings which partially be justified by the difference in the type of antidepressant, duration of treatment, technique of determining depression, and study setting [6, 8].

In the current survey, serum levels of IL-10 showed no significant differences neither in inter-, nor intra-group comparisons during the 8 weeks of treatment with sertraline which is in accordant with the findings of Taraz et al. [4] and in contrast with two early in vitro studies [9, 10].

Moreover, there are no significant differences in the studied biomarkers in sertraline responders and non-responders and might suggest that the anti-inflammatory effects of antidepressants appear to be independent to their efficacy for improvement of depression symptoms [4, 6].

The limitations of this study are small sample size, limited studied biomarkers with short half-life and the same doses of sertraline for responders and nonresponders.

In conclusion, the present clinical trial suggests that 8 weeks of sertraline therapy, independent of its antidepressive effects, significantly decreased the serum levels of IL-6 and CRP (but not IL-10), compared with placebo in depressed HSCT recipients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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