Reviewer's report

Title: Plasma levels of soluble cytokine receptors in euthymic bipolar patients with and without subsyndromal symptoms

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Reviewer: Alan Prossin

Reviewer's report:

The research question posed by the authors is understandable and novel in that the investigations involve the search for biological factors associated with sub-syndromal symptoms of Bipolar Disorder Type I. This is an understudied area and one associated with substantial clinical morbidity.

The data presented appear to reflect significant differences in 2 inflammatory measures when comparing well controls and volunteers with BD-I, but no difference is detected between the BD-I group with subsyndromal symptoms and the BD-I group without subsyndromal symptoms.

Major Compulsory Revisions:

However, there are various issues that would need to be described before concluding that the data presented are sound and/or well controlled.

1) It would be helpful if (perhaps via table) information were presented to describe the distribution of age, race, gender within the 3 identified comparator groups and to further describe treatments in much greater detail within the BD-I group. The authors do acknowledge the presence of medication treatment with broad classes of meds, but do not describe details as to specific meds being used, dose ranges, and frequency of polypharmacy, etc. Even if constraining medication treatment variables to broad classes (i.e. mood stabilizers, anti-depressants, antipsychotics), there would be some relevance in testing for class effects on inflammatory measures. These tests were not presented.

Further, there have been some attempts by other researchers to describe inflammatory effects of specific medications and/or to speak of specific medications in terms of medication equivalents in reference or a particular standard within that medication class (i.e. clozaril equivalents for atypical antipsychotic medications). While various problems exist with such investigations (i.e. one atypical antipsychotic potentially has vastly different inflammatory effects than another given the substantial receptor profile heterogeneity even within a particular medication class), the authors do not speak as to why such efforts have not been included in their investigations.

2) The authors refer to the inflammatory measures investigated as “pro-inflammatory markers”, but have not included pro-inflammatory cytokines (or other “pro-inflammatory” measures) in their investigations. While this reviewer agrees that the investigation of soluble cytokine receptors is fairly novel and in need of further investigation in mental illness in general and Bipolar Disorder in
particular, the authors do not provide sufficient justification for investigating soluble cytokine receptors. This is of particular importance given the authors’ stated desire to investigate “pro-inflammatory markers” and to conclude that their data evidences a “pro-inflammatory shift” in Bipolar Disorder while excluding pro-inflammatory cytokines from their investigations. While the reviewer agrees that soluble cytokine receptor concentrations may be reflective of the body’s attempt to reduce the impact of a pro-inflammatory shift, the data presented fails to show that the measured soluble cytokine concentrations in this population are directly proportional to measures of pro-inflammatory cytokines.

3) Additionally, the authors’ point in the discussion section that their results provide possible evidence of “ongoing pro-inflammatory processes,” in apparently euthymic BD-I volunteers is not supported to a great extent by their data. They have provided diagnostic differences in soluble cytokine receptors. This data is not longitudinal, medication effects are not controlled for, and it is unclear if the concentrations of soluble cytokine receptors that are measured are indeed a direct reflection of the volunteers’ pro-inflammatory cytokine concentrations as the latter have not been measured. Additionally, the authors conclude that they have not found differences in soluble cytokine receptor measures within the 2 BD-I groups (euthymic vs. euthymic subsyndromal). This reviewer would argue that it is difficult to comment on either negative or positive findings when testing for group differences given that medication treatment (and other factors) do not appear to have been controlled.

4) the authors suggest that they are testing for potential inflammatory markers of subsyndromal symptoms in BD-I, but have not presented data outlining such measures of clinical symptoms and whether such measures are related (i.e. correlated, etc.) to the inflammatory measures being investigated

Minor Essential Revisions:

1) would suggest to describe resulting inflammatory measures as concentrations rather than “levels”

2) would suggest to use language of comparison (i.e. higher, lower, etc.) rather than “increase” when describing group differences in inflammatory measures.

3) while this reviewer assumes that the individual soluble cytokine receptors were assayed via individual ELISA kits, it would be helpful in the authors added this detail to their description of the methods.

4) In the results section, the authors fail to present p-values of results that they report as having “no other differences”. It would be helpful if the authors would describe non-significant results as such, preferably including a p-value (i.e. p < 0.05).

5) A typo in the results section second paragraph: “either …. and” should be “either …. or”.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'