CORRESPONDENCE

Reply to Drs Munkholm and Paludan-Müller's comment on our paper "Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: results from a double-blind randomised clinical trial"

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In their comment, Dr Munkholm and Dr Paludan-Müller provide their interpretation of our subgroup analysis based on CRP threshold = 3 mg/L.

We thank the authors for contacting us in advance of their letter to discuss our study [1], and we were happy to address all of their questions, including clarifying that indeed the subgroup analysis was not prespecified in the published protocol of the study.

While we agree that the aforementioned analysis is explorative, we respectfully disagree with Munkholm's and Paludan-Müller's claim that a difference in effect between subgroups is uncertain.

First of all, we do fulfil one of the criteria mentioned by Munkholm and Paludan-Müller, as our subgroup analysis was supported by the presence of a significant interaction in the two-way ANOVA with CRP (above or below 3 mg/L) and study arm (placebo or minocycline) as factors, and changes in the HAM-D score as dependent variable ($F_{1-35} = 8.63$, $p = 0.006$). We are sorry we did not present this information in the paper.

Second, the difference between the subgroups is not only statistically significant but also clinically significant and large in magnitude, with effect sizes in the range of Cohen-d = 1.5–1.9. These are larger than the effect size ≥0.4 that is considered a clinically significant response criterion in previous clinical trials of antidepressant treatment employing HAM-D [2], and also larger than the effect size of the HAM-D differences between minocycline and placebo in a previous study on treatment-resistant depression (=1.2) [3].

Third, our subgroup analysis is supported by our data-driven ROC analysis, which identified a CRP threshold of 2.8 mg/L as cut-off for optimal minocycline-response, very close to our hypothesised threshold of 3 mg/L.

Fourth, we would like to highlight that this result is also biologically and clinically consistent with the notion that CRP levels above 3 mg/L indicate low-grade inflammation, associated with higher risk of both cardiovascular [4] and depressive disorders [5]. Moreover, a peripheral CRP > 3 mg/L has been found to be associated with elevated central (CSF) inflammatory markers [6] and with treatment resistance in depression [7].

In conclusion, we believe the effect of our subgroup analysis, albeit limited by the small sample size and the lack of pre-registration, is likely to indicate a true and clinically relevant effect, suggesting that peripheral inflammatory biomarkers, like CRP, could be useful in personalising minocycline therapy in patients with Major Depressive Disorder who do not respond to antidepressants. We certainly agree that our results will need to be replicated in larger samples, and it is indeed our intention to do so in our future research.

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AUTHOR CONTRIBUTIONS

MAN: conceptualization, methodology, writing. CMP: conceptualization, methodology, review, and editing. VM: conceptualization, review, and editing.

ADDITIONAL INFORMATION

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