Author’s response to reviews

Title: Youth Depression Alleviation with Anti-inflammatory Agents (YoDA-A): A Randomised Clinical Trial of Rosuvastatin and Aspirin

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REVIEWER 1: Giovanni De Girolamo

This is an important RCT on a topic of great interest, given the current paucity of effective treatments for youth depression. It should be published, but some issues should be solved and problems with the current manuscript should be tackled.

1. There was an impressive number of young people invited to join the study who declined to participate (N=500). Since the number is 4 times the number of enrolled subjects, they should explain this very high refusal rate, and possibly provide some info about the refusal sample (sociodemographic info, clinical characteristics, etc).

We thank the Reviewer for their suggestion and have included the following in the Discussion: “The sample size was relatively small, and was lower than planned recruitment based on the power analyses due to governance delay and operational issues, which could result in low statistical power to reliably detect between-group differences. A total of 1133 people who were approached were excluded, principally for not meeting inclusion criteria (n=583) and declining to participate in research (n=550).”

2. On page 14 they state that the sample size needed to power the study was N=270: if so, they started the trial with a sample which was exactly as half as the sample deemed as necessary. This questionable procedure should be explained in some ways, because starting a RCT being already aware at the start that the power will be not large enough to allow a meaningful answer to study questions raises interesting ethical issues.
As above, there was a substantial delay in the governance approval process, which resulted in the clock ticking without being able to recruit. This was the major reason for the recruitment difficulties, which limited time to recruit as budgets were fixed. This has been clarified as above.

3. On page 17 they report that while RESPONSE rates in the 3 groups were rather different, on the contrary REMISSION rates were surprisingly strikingly similar: they should comment this finding.

We thank the Reviewer for this observation and have included the following statement in the Discussion: “Nevertheless, there were no differences in remission rates between groups. While remission rates were similar across treatment groups, response rate ranged from 25% to 45.8%. In 30 cases (5 cases in aspirin, 16 cases in rosuvastatin and 9 cases in placebo), while there were more than 50% reduction from baseline at week 12 (MADRS response), the absolute value of MADRS score at week 12 was more than 7 (i.e. no remission). Baseline MADRS score for these 30 cases was 32.3 (5.6).”

4. A MAJOR problem with the study, which has surprisingly been totally omitted, is that the experimental treatment was an ADD-ON to ongoing treatments. Needless to say, this may greatly confound the results, but the authors do not say anything about this. While they have done a lot of secondary analyses, they have not done any subgroup analyses stratifying between subjects taking or not taking ADs, undergoing or not undergoing psychotherapy, or doing combined treatment with AD + psychotherapy (if any). This info is of utmost relevance and these analyses should definitely be added, although the small sample can certain limit the conclusions to be drawn. In addition, it would be interesting to add a table with some info about the ongoing treatments: if possible, type of AD prescribed, mean dosage, type of psychotherapy, duration, etc.

We thank the Reviewer for this observation. ADD-ON to ongoing treatments/history of treatment was examined through additional GEE models that evaluate the interaction between these items and MARDs improvement across treatment groups. We have explained the evaluation method in the Statistical analyses section of the Methods: “The impact of baseline treatment characteristics including number of concomitant medications during the trial, psychotherapy or antidepressants was examined from a separate GEE including all measurement time points (excluding week 26) using the same methods as previously outlined.” The findings of this evaluation method are reported in the Results section: “Baseline treatment characteristics such as number of concomitant medications during the trial, psychotherapy or history/ ongoing sue of antidepressants did not significantly affect these results.” In addition, two supplementary tables (S5 and S6) were added to the Supplementary Appendix explaining history and ongoing antidepressant therapy and psychological therapy across trial arms.
5. Table 3 should be included as SUPPLEMENTARY table, because it is very long and does not provide any striking results.

Table 3 (Secondary outcome measures comparing Rosuvastatin and Aspirin to placebo; with 12 weeks follow-up as the primary comparison) has been included in the Supplementary Appendix (Table S3).

REVIEWER 2: Michele Fornaro

Overall, I really enjoyed reading the present report, which I found impeccable, especially in terms of methodology and interpretation of the results, Therefore, my remarks should be merely intended as discrentional suggestions for the authors, to whom I compliment for their efforts.

1. The primary outcome of the study was "change in MADRS" score at w12 vs. baseline. I would also suggest to append the rate of responders defined as the proportion of cases who achieved at least a 50% score reduction vs. baseline records, since I think that would be more informative than the SMD indexes (which, by the way, I did not see reported). Thank you.

We thank the Reviewer for their suggestion. Remission and response were defined in the a-priori Statistical analyses plan, as described in the Methods on page 15: “Remission and response analyses were conducted by dichotomising the MADRS score using cut-off scores of seven or less for remission, and more than 50% improvement compared with baseline for response, respectively”. The standard mean differences were not an a-priori outcome and therefore not reported in the manuscript.

2. I think the discussion should further stress-out the fact that anti-inflammatory agents for depression could be used at low-to-moderate doses when prescribed as augmentation strategies for established antidepressants (e.g. previous reports for sertraline add-on), even when monoamine-modulating antidepressant do not lead to satisfactory responses. This is something to study in forthcoming RCTs comparing an antidepressant plus placebo or plus an anti-inflammatory agent. Ideally, that may also save some dose of the augmentation agent, thus resulting in lower discontinuation rate attributed to side effect (tolerability).
We thank the Reviewer for their comment and have included the following statement in the Conclusion: “Anti-inflammatory agents for depression could be used at low-to-moderate doses when prescribed as augmentation strategies when monoamine-modulating antidepressants do not lead to satisfactory responses”.

3. I appreciated the GEE option instead of the GLM and the explanation why.
We thank the Reviewer for this feedback.

4. The computed sample size is 270 or more, however 130 were randomized.
We thank the Reviewer for their comment. As reported in the CONSORT diagram (Figure 1, page 36), a number of potential participants were ineligible (n=583) or declined to participate (n=550). We have reported the following statement in the Discussion: “The sample size was relatively small, and was lower than planned recruitment based on the power analyses due to governance delay and operational issues, which could result in low statistical power to reliably detect between-group differences. A total of 1133 people who were approached were excluded, principally for not meeting inclusion criteria (n=583) and declining to participate in research (n=550).”

REVIEWER 3: Pao Lin

The aim of this study was to compare adjunctive aspirin and rosuvastatin with placebo in youth depression with usual care. Overall, this study is well conducted. Research rationale is well described. Study procedures and results are well reported. I have some comments below.

1. Young people have less prevalence of major systemic diseases than adults and elderly people, and thus may have lower inflammatory response than older age groups. If this is correct, do authors expect to see a positive effect of aspirin and rosuvastatin in youth depression more than placebo? Moreover, is it speculated that elderly people with depression will be benefited from treatment with anti-inflammatory agents? I expected to see more discussion about this age factor.
We thank the Reviewer for their observation and we have included the following statement in the Introduction: “Depression not only is associated with depression in youth, but risk factors for depression themselves, such as trauma and obesity, are associated with inflammation.18, 19…In adolescent depression, inflammation is predictive of therapeutic response, suggesting a core role of these pathways.21”

2. Do patients receiving concomitant antidepressant drugs or psychotherapy respond better or worse from aspirin or rosuvastatin? This information is expected from collected data.

We thank the Reviewer for their comment and have included the following explanation in the Secondary outcomes section of the Results: “Baseline treatment characteristics such as number of concomitant medications during the trial, psychotherapy or history/ongoing use of antidepressants did not significantly affect these results.”

3. Authors are expected to explain why to use age, BMI, depression severity, and number of MDD episodes as the factors for subgroup analysis.

We thank the Reviewer for their comment and have included a statement explaining the characteristics used in the subgroup analysis in the Statistical analyses section of the Methods: “Additional subgroup analyses for age (&lt; 18 vs. ≥ 18 years), BMI (&lt;30 vs. ≥30), severity using the QIDS (QIDS&lt;20 vs. QIDS≥20), and number of major depressive episodes (MDD episodes≤2 vs. MDD episodes&gt;2) were performed. These subgroup analyses were selected based on the literature suggesting that these are potentially predictive demographic characteristics.63-65 The impact of baseline treatment characteristics including number of concomitant medications during the trial, psychotherapy or antidepressants was examined from a separate GEE including all measurement time points (excluding week 26) using the same methods as previously outlined.”