Reviewer's report

Title: Corticosteroid therapy in regressive autism: A retrospective study of effects on the Frequency Modulated Auditory Evoked Response (FMAER), language, and behavior

Version: 4 Date: 7 March 2014

Reviewer: Deborah Fein

Reviewer's report:

This paper continued to address a very important topic in the treatment of a group of quite severely affected children, and the main point, that an RCT is needed, is amply made. The manuscript is certainly much improved. Some needed detail and explanation is added, and conclusions are considerably softened. I am still quite troubled by the likelihood that some parents and physicians will leap to treatment. I consider the following points minor essential revisions.

1. Specifically, I am troubled by the dissimilarity of the control group to the STAR group, and the language and behavior ratings, which are not validated measures and done with full knowledge of the treatment the child is under, but at least the claims are softened accordingly; if I were editing this paper, I would soften them a bit more, especially with regard to comparison of language and behavior in the two groups (see below).

2. I would add some points to the limitations: The authors do say: Aside from the FMAER, language and behavior description transformed into quantitative data were obtained by by clinicians in collaboration with the parents. …Neither of the language measures is standardized or published’. However, equally serious is the fact that the parents and clinicians who rated the child’s language were fully aware of the steroid treatment and quite possibly invested in the outcome. As I may have mentioned in my first review, I frequently see parents whose children are undergoing a treatment of some kind, who report great improvement, which fails to materialize upon formal testing. While the FMAER and EEG readings were done blindly (I believe), the language and DSM symptom- behavior ratings were definitely not, in the sense that the clinicians and parents knew about the child’s treatment.

3. Furthermore, the paper asserts that ‘Neurologists using the CLSQ are sensitive to the language performance definitions in question and trained to reliability in score assignment’. Unless there are data to back up this claim of reliability, I would delete it.

4. Along the same lines of my discomfort with the control group, especially with regard to changes in behavior and language (less so with the FMAER and EEG changes), the authors state: Moreover, significantly more STAR group subjects (17/20) than NSA group subjects showed improvement (6/24 ‘better’ receptive, and 10/24 ‘better’ expressive). These data suggest that steroid treatment may be
associated with improvement in language and that more subjects who receive steroid treatment may show such improvement than subjects in the non-treated group.’ I appreciate that all such statements are now qualified with ‘may show’ but I still think this is overstated, especially ‘…that more subjects who receive steroid treatment…nontreated group.’ The control group was quite different in many regards from the STAR group – they were mostly non-regressive, it is not clear that demographics were matched in any way – this is indeed a convenience sample. The only real basis for this comparative statement would be to take similar groups of children and treat one and not the other, based on something approaching random assignment and not clinical judgment and parent willingness. Even an open trial with better matched control and experimental groups might warrant the cautious claim, but the really unmatched groups do not seem to warrant it. In other words, I appreciate the qualifications but I don’t think they really go quite far enough.

5. I previously raised the question of additional treatments for either group. The ms. now states ‘Post hoc record review revealed that none of the STAR group children received any additional pharmacological, behavioural, or educational interventions during the steroid treatment period.’ This is extremely unlikely, at least I hope it is. These are 3-5 year old autistic children receiving treatment for an average of 9 months, to a maximum of 14 months. Surely, they were in behavioral or other educational interventions during this time, and not sitting at home? If these data are not available, that could just be stated as a limitation.

6. Some smaller writing issues: I would add the average length of treatment to the abstract, so the reader has a better idea of the scope of the study.

7. ‘More STAR group children showed significantly improved behavior scores after the steroid treatment period as compared to before the treatment.’ More than what? The untreated group?

8. I my original review I noted with regard to the title of Table 6: ‘Effect of steroids on CLSQ difference scores for STAR group’, that this is really misstated – these data are not the effect of steroids – they are change in score over time, which the authors are attributing to the use of steroids. The authors replied: This is correct and the Table title and text have been modified. However, in the version of the Tables in the supplementary material that I had access to, the title does not appear to have been changed.

9. Table 11a: see text and Table XX – XX needs to be fixed.

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