Reviewer's report

Title: Rapid improvement in verbal fluency and aphasia following perispinal etanercept in Alzheimer’s disease and semantic dementia

Version: 4 Date: 3 June 2008

Reviewer: Ian Clark

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The literature, as well as this text, indicates that for some period now this group has been producing evidence consistent with etanercept, a synthetic TNF p75 receptor construct, being efficacious in Alzheimer's disease. The background literature is there, and the route is novel and plausible. As someone who has been, since its inception (Cytok. Gr. Fact. Rev., 18, 335-343. 2007, How TNF was recognized as a key mechanism of disease) involved in the broader pattern of disease that TNF can initiate, this encouraging result in a new area of disease does not surprise me. Nor does it surprise me that the large established players in the field have given this small group of privately-funded outsiders, who are not in the position to recruit patients for random allocation in controlled trials, but can simply advocate them, as they have done here, a hard time in the popular press and internet. This should not influence the science, or a fair hearing for this potentially very great advance.

The data are limited, but these limitations are clearly defined. I regard the conclusions amply supported by the data. The video-taped interrogation of the patient’s relative is an impressive and convincing tool in this subtle and complex disease. Other points on your journal’s checklist, such as acknowledging the work of others, writing acceptability and the abstract accurately conveying the story are acceptable.

Suggested discretionary revisions are:

The number of references in the 1-22 group is unusually high, but they do make a point, and their tolerance is an editorial rather than a scientific issue. The first sentence of the second paragraph of the Background could usefully include a reference to the introduction of etanercept. Although lymphotoxin as yet has a no directly relevant literature, it could be noted, in the text, that etanercept also suppresses the actions of this cytokine, since its action depends on the same p75 receptor as does TNF. Logically this also requires a reference.

Minor essential points of revision points detected were:

1. Reference 28 shows a 2003 paper, not the expected submitted text spoken of in the text (which I suspect should be shown in the manuscript, not listed at the end).

2. In Acknowledgements, the wording should be altered to be consistent with
there being a single family member who made videotaped comments.

3. The caption of Fig. 2 should refer to case report 2, not case report 3.

4. Some reference titles are in title case, others (most) in lower case. No doubt the journal has a policy of one or the other.

I have no major compulsory revisions. In summary, my view is that such off-label originality, with large and clinical scientific potential, should, in my opinion, be aired in the literature, and given the chance to generate the Phase III trials the authors advocate.

**Level of interest:** An article of outstanding merit and interest in its field

**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.