

LETTER TO THE EDITOR

Comment on alemtuzumab and inclusion body myositis

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Sir, The recent *Brain* publication (Dalakas *et al.*, 2009) describing a clinical study of alemtuzumab in patients with inclusion body myositis nicely demonstrates the feasibility of enrolling and following a cohort of these patients over a long period of time as participants in an intervention study. The authors state that 'in [inclusion body myositis] one series of alemtuzumab infusions can slow down disease progression up to 6 months'. Prior to publication of this paper in *Brain*, two scientific meeting abstracts and an editorial similarly reported results of this study as showing that, in inclusion body myositis, alemtuzumab may have a role in improving the clinical condition of patients (Dalakas *et al.*, 2007a, b; Dalakas, 2008). Based on the Methods and Results now published in *Brain*, I have concerns that these conclusions may require further analysis for several reasons.

- (i) According to the National Institute of Health ClinicalTrials.gov registration (<http://clinicaltrials.gov/ct2/show/study/NCT00079768>), the primary endpoint target was a 15% change in muscle strength, yet the Dalakas *et al.* (2009) paper adopts a 10% change. The 15% endpoint was first entered into the ClinicalTrials.gov registration on 20 June 2006 at which time at least eight participants had already completed the study (Dalakas, 2006), through an amendment to the registration (http://clinicaltrials.gov/archive/NCT00079768/2006_06_20). Because several outcomes reported in the Dalakas *et al.* (2009) paper fail to meet this 15% target but do meet the 10% target (e.g. the 13% differential mean change in quantitative muscle strength testing; the comment regarding four participants with a mean increase of 10% in quantitative muscle strength testing; and the 11.4% mean manual muscle test change), there is an appearance of using post-trial target

endpoint alteration to support efficacy. One purpose of advanced trial registration is to make public the outcome endpoint targets before data are analysed in order to improve study transparency; and this is often a condition of subsequent publication (Laine *et al.*, 2007).

- (ii) Analyses of primary outcome measures are the gold standard in clinical trials upon which claims of efficacy are established. In this study, the primary outcome muscle strength 'quantitative muscle strength testing' decline over a 12 month untreated period (−14.9%) is compared with a quantitative muscle strength test decline over a 6 month post-treatment period (−1.9%), with a statistically significant 13% difference reported. However, patients with any progressive disorder are likely to decline more over a 12 month than a 6 month period, even without intervention. What should be reported is the magnitude and statistical significance of the quantitative muscle strength test decline over the 6 month period prior to treatment, compared with the 6 month period after treatment; such data were collected according to the Methods but not reported. The correct 6 month difference comparison is probably smaller in magnitude and possibly not statistically significant.
- (iii) As with the quantitative muscle strength testing data, changes in the other primary outcome (manual muscle testing) data over 12 and 24 month untreated periods are compared with the decline over a 6 month post-treatment period. Again, what should be compared is the manual muscle testing data 6 months prior to treatment and the manual muscle testing data 6 months after treatment. Additionally, it is not clear where the 24 month untreated manual muscle testing data presented in the text and in

Fig. 2 (which implies that such data are present for all 13 participants) come from because, according to the Methods, such natural history data were obtained for up to 12–18 months.

- (iv) According to the National Institute of Health ClinicalTrials.gov trial registration, these participants received lymphapheresis just before treatment with alemtuzumab, an intervention that may have confounded the efficacy results, yet this was not mentioned in the Dalakas *et al.* (2009) paper. Lymphapheresis typically removes both plasma and lymphocytes, the same population targeted by alemtuzumab. It is used in the treatment of several autoimmune diseases, where its mechanism of action might relate to removal of cells, plasma or even alteration of blood cells returned back to the circulation. Even a single treatment is a potential confounder for the interpretation that efficacy effects were exclusively due to the use of alemtuzumab, since this procedure, never reported as studied in inclusion body myositis, could conceivably have a modest and temporary effect on slowing disease progression. Because of this intervention, it is not possible to attribute efficacy in this study to alemtuzumab alone.
- (v) Another potential confounding issue relates to these participants having received daily valganciclovir for several months. This anti-viral agent has never been evaluated in inclusion body myositis and its potential effects should be kept in mind. For example, the authors have previously considered the possibility that inclusion body myositis is caused by chronic viral infection (Dalakas *et al.*, 1998). According to the Methods, valganciclovir was administered 'upon initiation of treatment and up to 6 months thereafter or until the absolute lymphocyte count was >500 cells/ μ l, whichever occurred later'; so that all participants received daily valganciclovir for at least 6 months (the point at which primary outcome measures are compared with natural history data) and some (#4 and #5) for at least 10 months. The contribution of treatment with valganciclovir was not discussed; as with the lymphapheresis treatment, its use may affect the interpretation that efficacy was due to alemtuzumab alone.
- (vi) The Dalakas *et al.* (2009) paper states that depletion of peripheral blood lymphocytes 'persisted up to 6 months', reiterating previous publications by these authors (Dalakas *et al.*, 2007a, b). My concern is the possibility of prolonged lymphopaenia with regard to safety; substantial reduction in blood lymphocyte counts persisted for much >6 months, as shown in Table 1, where lymphocyte counts for the 13 participants were at a mean of 31% of pretreatment values at 6 months, 41% at 8 months, 48% at 10 months and 55% at 12 months. At 10 months, two participants still had peripheral blood lymphocyte counts low enough (<500 cells/ μ l) that they were receiving anti-viral prophylaxis. Upon completion of this study, one year after alemtuzumab treatment, participants had a mean 55% of their pretreatment peripheral blood lymphocytes; one participant had only 37% of his/her pretreatment level.

- I am unsure as to why 6 months was chosen to represent the extent of reporting blood lymphocyte depletion. This issue is important because the 6 month claim is used to further an argument that the study was unbiased because 'the gains in strength lasted ~ 6 months, coinciding with the effect of CAMPATH on T cell depletion'.
- (vii) Some data from the study were previously reported in two published meeting abstracts (Dalakas *et al.*, 2007a, b). In both of these presentations, 6 of the 13 participants were reported as having positive quantitative muscle strength test changes (increases in strength), ranging from 4%–35%. In the Dalakas *et al.* (2009) publication, only 4 of the 13 participants are reported as having positive quantitative muscle strength test changes, ranging from 4%–19%. One participant, twice previously reported as having a 35% improvement in strength, is reported as having a decline in strength. If the meeting abstracts are in error due to a change in two participants' outcome data on completion of the study, appropriate corrections should be considered.
- (viii) It is stated that '[quantitative muscle strength testing] measurements were reinforced with the MRC data', as measured in the second primary outcome manual muscle testing score. However, it is possible to interpret a conflict in these data, since both are measures designed to capture the same concept ('muscle strength'), yet quantitative muscle strength testing scores worsened (–1.9%), whereas manual muscle testing scores improved (+11.4%). The discrepancy in the quantitative muscle strength testing and manual muscle testing data suggests that assessment bias might be present, as the manual muscle testing measure is probably more susceptible to such bias (see below).
- (ix) Two important concerns in unblinded, non-placebo controlled studies such as this are (a) assessment bias; and (b) the placebo effect. The authors do consider the possibility of bias through unblinding, stating that it was not present and presenting six reasons for this. However, none of these points specifically address assessment bias. For example, although the first reason given is that 'the evaluators performing the [quantitative muscle strength testing] examinations were not participating in the day-to-day activity of the patients', this would not reduce the assessment bias of evaluators when positioning and instructing participants for quantitative muscle strength testing. Therefore, the view that these results are unbiased could be seen to conflict with basic principles that dictate the need for blinded trials to assess intervention efficacy.
- (x) The authors state that with regard to participants' subjective reporting of daily activities 'some placebo effect cannot be excluded'. However, placebo effects are not limited to self-reporting but can be seen in many so-called 'objective' measures of function. Although placebo effects have never been reported in the specific context of manual muscle and quantitative muscle strength testing, it seems possible that a participant given alemtuzumab with an expectation that it will increase strength may then increase their performance on these tests in the absence of an underlying biological effect.

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