

LETTER TO THE EDITOR

Reply: Comment on alemtuzumab and inclusion body myositis

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Sir, Dr Greenberg misinterprets several important aspects of our study, including the scope and applied methodology. Below we have addressed the points raised in his correspondence.

This was a proof-of-principle molecular clinicopathological study designed to investigate the effect of alemtuzumab on endomysial T cells and disease progression; it was not primarily a trial of clinical efficacy. As stated, alemtuzumab did not significantly improve patients' strength and function but only induced short-term stability based on the difference between two time periods. Contrary to Dr Greenberg's comments, outcome was not based on any predetermined percentages that were subsequently amended. The percentages mentioned by Dr Greenberg were used only to power the sample size. As our results show, these percentages do not relate to the outcome or conclusions of the study because, regardless of whether a 10%, 13% or 15% difference is used, there is no significant improvement in the patients' strength (as he correctly points out, only 4 of 13 patients improved, by only 4%–19%, while the mean strength for all patients declined by 1.9%).

Our data and the interpretation of results have now been ratified in an independent review by the National Institutes of Health. The main finding was a significant reduction of relevant molecules seen in repeated muscle biopsies, combined with short-term clinical stability; this is encouraging and, as we stressed, warrants a controlled study. One should not read more than that from these results. The study was arguably small and uncontrolled but taught us a lot about the pathogenesis of inclusion body myositis; it was not designed to demonstrate

clinical efficacy and we do not recommend alemtuzumab as a treatment for inclusion body myositis.

Regarding Dr Greenberg's specific points (and necessarily restating some of our general responses already outlined), our comments are as follows:

- (i) Introduction to his letter and points (i) and (vii): we had indeed reported, at two scientific meetings 2 years ago, preliminary data showing that 6 of 13 patients improved by 4%–35%. In the *Brain* paper, we reported that only 4 of 13 patients improved, by only 4%–19%. This indicates: (a) care in the final analysis which was repeated several times to ensure accuracy; and (b) publication of unbiased data, describing a lower number of patients that gained strength, rather than overinflating the results. There was no statistical improvement in the patients' strength, regardless of whether a 10%, 13% or 15% predetermined change was used during analysis. We did not suggest that such a minor change was significant. The clinical end-point was the induction of 6 months stability, based on the difference between the two time periods, not a predetermined percentage change. The percentages of 15% and 10% that Dr Greenberg mentions were only used to calculate the sample size. As stated in our manuscript, when referring to the number of patients needed, 'power analysis was not performed for detecting changes in disease progression as the percentage of strength decline was not

known at the time the protocol began'. The arbitrary 15% change was mentioned in the original protocol to calculate a conservative sample size. Because stability, not improvement, was the primary target of the study, we estimated—based on the early quantitative muscle strength testing observations which showed <5% variability from test to test—that a 10% change was sufficient to capture stability and complete the study with a smaller number of patients. Terminating the study with a lesser number of patients was communicated to the Institutional Review Board. The web site at clinicaltrials.gov, quoted by Dr Greenberg, lists only the original abstract of the study. This web site is renewed automatically only to bring the registration up to date by the National Institutes of Health Clinical Centre, without further input from the investigator.

- (ii) Points (ii) and (iii): we did compare the decline of 12 months to that of a change observed after 6 months of treatment. We feel that these comparative periods are the most appropriate to capture meaningful changes because previous studies have not shown much decline over a 6-month natural history period (Rose *et al.*, 2001). Therefore, we do not feel that comparing the changes to those of 6 months would have been more meaningful clinically.
- (iii) Point (iv): one episode of lymphapheresis, prior to the study, will not affect the efficacy of alemtuzumab 6 months later because: (a) as shown in a previous controlled study, lymphapheresis has no beneficial effect in inflammatory myopathies, even if given as several courses (Miller *et al.*, 1992); and (b) there was no resultant significant reduction of lymphocytes causing a long-lasting effect, which might have contributed to the effects of alemtuzumab.
- (iv) Point (v): the suggestion that the prophylactic administration of valgancyclovir may have confounded the results is unlikely to be correct. Although we have theorized that inclusion body myositis may be triggered by a virus, neither we, nor others, have identified DNA viruses in muscle biopsies from patients with inclusion body myositis.
- (v) Point (vi): the noted peripheral blood lymphocyte reduction initially starts as a depletion. We chose the 6 month period because previous studies have shown consistent reductions up to that point. Since this was a clinicopathological study, we also chose the 6 month period as the best time to assess any reduction of endomysial lymphocytes in the repeated biopsies and any changes in clinical measurements.
- (vi) Point (vii): we briefly addressed the difference between quantitative muscle strength testing and Medical Research Council measurements in the paper. It is well known that all methods of muscle strength assessment, from

computer-assisted to manual techniques, have inherent limitations. Given the differences in positioning, precision, scoring criteria and scale of measurement, it is not surprising that the quantitative muscle strength and Medical Research Council scoring do not reflect equivalent changes in strength (Tiffreau, 2007). One of several things we learned from this study is the importance of having a performance-based functional assessment. Future studies will favour performance-based functional measures in addition to impairment-based outcomes, to assess clinical changes. Such scales have been used both in amyotrophic lateral sclerosis trials and in multiple sclerosis trials for a long time. There is already a good effort to create such scales in inclusion body myositis (Jackson *et al.*, 2008).

- (vii) Points (ix) and (x): we agree that assessment bias and placebo effect are important factors but both are unavoidable in uncontrolled studies. This is the reason we stated in the paper that a 'placebo effect could not be excluded' and recommended a controlled study.

We are enthusiastic about exploring further the use of alemtuzumab based on the significant short-term stability that we describe. Since publication, the *National Institute of Neurological Disorders and Stroke* requested an independent review of our paper and we are happy to confirm that the results have been independently verified; and our main message, that 'the rate of strength decline 6 months after alemtuzumab was significantly reduced compared with the 12 month natural history period' was ratified.

The significant modulation of relevant molecules in the repeated muscle biopsies, along with the noted strength gains in some patients, has been informative with respect to the pathogenesis of inclusion body myositis. We are pleased to have completed a difficult clinicopathological study, one of the few of its kind, and grateful to all our patients for contributing to the study.

References

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