**INTERFERONS HAVE BEEN SHOWN TO PREVENT LONG TERM DISABILTY: IT REMAINS UNCERTAIN**

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There can be no reasonable doubt that the primary and key target for multiple sclerosis therapy would be the prevention of the onset of the progressive disease and long term disability. After all, it is unremitting disability that accounts for the medical, social and economic negative impacts of MS. Both clinical and MRI surrogates or biomarkers have recently failed elementary validation steps.

The disability measures were evaluated in a large placebo sample from the Sylvia Lawry Centre database and the abstract of a paper which appeared in the Aug 26th issue of Neurology follows.

Inferences about long-term effects of therapies in multiple sclerosis (MS) have been based on surrogate markers studied in short-term trials. Preventing progressive disability is the key therapeutic goal but there remains no validated definition for its measurement in a trial context. Meanwhile, MS trials continue to shorten and to depend on unvalidated surrogates. Since there have been no treatment claims for improving unremitting disability, worsening of disability in the placebo/control arm must occur for effectiveness on this outcome to be shown.

METHODS: We examined widely-used clinical surrogates of long-term disability progression in individual MS patients within a unique database from the placebo arms of 31 randomised clinical trials.

RESULTS: Detection of treatment effects in secondary progressive MS trials is undermined by noise in disability measurement. Whereas existing measures can be partially validated in secondary progressive MS this is not the case in relapsing-remitting MS. Here, examination of widely used definitions of treatment failure demonstrated that disability progression was no more likely than similarly defined improvement. Existing definitions of disease progression in short-term intervention trials in relapsing-remitting patients reflect random variation, measurement error and remitting relapses.

CONCLUSION: Clinical surrogates of unremitting disability used in trials of relapsing-remitting MS cannot be validated. Trials have been too short or degrees of disability change too small to measure the key outcomes. These analyses highlight the difficulty in determining effectiveness of therapy in chronic diseases.

*It is clear that disability measures will have to be more stringent than they have been before in the main clinical trials over the last 1-2 decades. These considerations influence the persuasiveness of data aimed at answering the question of long term efficacy for any therapy. Ongoing studies which examine outcome in the context of natural history studies may help resolve these key clinical issues.*

Similar evaluation has been carried out for the MRI measures widely used in trials. The paper outlining these assessments will soon be published and it demonstrates that MRI adds no predictive value for relapse prediction to the much maligned historical relapse rate. Similarly for measures of T2 burden there is little indication that this adds to banal clinical measures of disability which as currently employed are in need of fortification themselves.

These results make it clear that additional effort will be needed to establish outcomes that are validated.

The main difficulty in establishing long term efficacy does extend beyond the outcomes themselves and by the time hard outcomes of disability are reached trial data even with followup can be plagued by dropouts and differential compliance.

There is no substitute at this point for randomisation and blinding which are sacrificed in followup studies and attempts at complete ascertainment should continue. Intention to treat and intention to scan analyses should be essential requirements for studies aiming to establish long term efficacy.