WriteClick: Editor's Choice

Editors' Note: Submissions to WriteClick this week highlight a common difficulty: how to relate conclusions from research to clinical practice and vice versa. Dr. Ebers and colleagues debate with authors Sormani and De Stefano about the article "Combined MRI lesions and relapses as a surrogate for disability in MS," with a sticking point over the difference between surrogacy and correlation. They agree in calling for another look at the outcomes used in multiple sclerosis trials. Drs. Kent and Mandava, in reference to "Predicting outcome of IV thrombolysis-treated ischemic stroke patients: The DRAGON score," point out the difficulties inherent in using multivariate analysis of large datasets to create outcome prediction models.

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COMBINED MRI LESIONS AND RELAPSES AS A SURROGATE FOR DISABILITY IN MS

George C. Ebers, Oxford, UK; Antonio Scalfari, London; Martin Daumer, Munich; Christian Lederer, Munich: Sormani et al.[1] claim to have validated individual-level surrogacy of MRI lesions/relapses for Expanded Disability Status Scale (EDSS) worsening. However, the outcome measures (greater than 1 EDSS point change over 2 years) used during PRISMS are mostly if not entirely noise, and do not relate to true unremitting disability.[2] The conclusions of Sormani et al. conflict with results from the London, Ontario (LO) database, showing equal times to hard endpoints (DSS 6 and 8) among untreated patients with low (1–2), intermediate (3–4), and high (greater than 5) number of attacks during the relapsing-remitting phase.[3] In addition, data from 31 placebo arms demonstrated no significant correlation between T2 MRI lesions and disability accumulation.[4] These results invalidate relapses and MRI changes as surrogate markers for disease progression. The authors suggest that heterogeneity of data in observational studies makes results difficult to compare. The variability of outcome in the LO database population[3] reflects the natural variation of disease course and the high quality of the study methodology. Heterogeneity among MRI sites, on the other hand, is not mentioned.[5] Although Sormani et al. discuss the limitations of their findings their conclusions are overstated. It is time to rework the outcomes used in multiple sclerosis (MS) trials and to improve their methodology.

Author Response: Maria Pia Sormani, Genoa; Nicola De Stefano, Siena, Italy: We validated surrogacy of MRI lesions/relapses for EDSS worsening, the only clinical measure accepted as a true measure of outcome by regulatory agencies. We agree that EDSS is largely insensitive (i.e., noisy) and this makes finding surrogacy for MRI lesions/relapses more difficult. Ebers et al. keep confounding correlation with surrogacy. A surrogate is a marker to predict the effect of a treatment on the clinical endpoint of interest and surrogacy cannot be evaluated outside of a treatment trial. Therefore, the lack of correlation in uncontrolled studies, as in those cited by Ebers et al., is not informative: the absence of evidence cannot be confounded with the evidence of absence.[6] We agree with Ebers et al. that it is time to rework the outcomes used in MS. This should start from clinical measures, which are largely more insensitive and noisy than MRI measures, especially if they are coming from old databases.

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2. Ebers GC, Heigenhauser L, Daumer M, Lederer C, Noseworthy JH. Disability as an outcome in MS clinical trials. Neurology 2008;71:624–631.
3. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain 2010;133:1914–1929.
4. Daumer M, Neuhaus A, Morrissey S, Hintzen R, Ebers GC. MRI as an outcome in multiple sclerosis clinical trials. Neurology 2009;72:705–711.
5. Schach S, Scholz M, Wolinsky JS, Kappos L. Pooled historical MRI data as a basis for research in multiple sclerosis: a statistical evaluation. Mult Scler 2007;13:509–516.
6. Altman DG, Blend JM. Absence of evidence is not evidence of absence. BMJ 1995;311:485.