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Plasmapheresis: are bigger studies necessarily better?

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I read with interest the comments of Professors Hughes and Hartung regarding the use of plasmapheresis to treat neurological disorders based on the most recent American Academy of Neurology (AAN) practice guideline (Neuroimmunology: Assessing the value of plasma exchange in neurology. *Nat. Rev. Neurol.* 7, 309–310; 2011).[1] I was disappointed to see that the authors did not cite our class II study,[2] referenced in the AAN practice guideline,[3] which provides strong support for the use of plasma exchange to treat acute, severe relapses of inflammatory demyelinating disease that are refractory to standard treatment with corticosteroids.

Our study was a randomized, double-blind, sham-controlled evaluation of 22 patients with severe corticosteroid-refractory attacks of inflammatory demyelinating disease.[2] The study design included a crossover, allowing both intrapatient and interpatient comparisons of response to active and sham plasmapheresis treatment. The outcomes required to declare success in this study were moderate to marked improvements in neurological deficits. Largely on the basis of this study, the Therapeutics and Technology Assessment Subcommittee of the AAN reached the following recommendation: "plasmapheresis may be considered in the treatment of fulminant CNS demyelinating diseases that fail to respond to high-dose corticosteroid treatment (Level C)."[3] The main concerns that limited a higher rating of the evidence were the small size of the study and the heterogeneity of the inflammatory demyelinating diseases that were included in the study. Inflammatory demyelinating diseases are notoriously difficult to accurately classify at initial presentation.[4] For example, acute transverse myelitis may occur as a non-recurring entity or as part of acute disseminated encephalomyelitis or, on the basis of further follow-up, may be reclassified as an initial attack of multiple sclerosis or neuromyelitis optica.

One of the key messages of our study[2] is that the exact classification of demyelinating syndrome does not matter greatly in terms of acute treatment of an attack: favourable responses occurred throughout the steroid-refractory CNS inflammatory diseases that we evaluated. Subsequent retrospective analyses have similarly supported the use of plasma exchange in a variety of demyelinating syndromes,[5–9] as have prospective uncontrolled studies in diverse CNS demyelinating diseases.[10–12] As noted by Hughes and Hartung, attacks of inflammatory demyelinating disease improve spontaneously, confounding the reliability of studies that target a broader population of these patients. Our study[2] was a focused study concentrating on the subgroup of patients who failed to respond to steroids, the subgroup of greatest concern to clinicians treating these diseases. Although failure to recover from an attack of demyelinating disease is an uncommon situation, it is certainly one that occurs with sufficient frequency to create a substantial clinical challenge to clinicians caring for patients with these conditions. It is a particularly common challenge in severe inflammatory demyelinating diseases such as neuromyelitis optica that our group has been able to define.[13] Large positive studies that include all patients with relapses of inflammatory demyelinating disease would certainly provide robust support for plasmapheresis in this setting and would impress Cochrane reviewers.

We agree that small subgroup studies such as ours should be confirmed by further studies. We also believe that it is a mistake to ignore small, effectively blinded and well-focused studies performed in a subgroup of patients, especially when targeting serious acute illnesses with major neurological deficits. We do not believe, however, that large randomized studies are required in such patient subgroups before the results are acceptable to guide everyday practice. Focusing only on the equivocal results of large studies in unselected and fundamentally uninformative groups of patients with limited power may prevent the appropriate patients from receiving beneficial treatments that significantly reduce morbidity.

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Competing interests
The author declares an association with the following company: RSR. See the article online for full details of the relationship.

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