EDITORIAL OPEN ACCESS

Plasmapheresis for acute attacks in neuromyelitis optica spectrum disorders

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Neurol Neuroimmunol Neuroinflamm 2018;5:e510. doi:10.1212/NXI.0000000000000510

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The focus of treatment in MS is trending away from interventions for acute relapses, but surprisingly, the opposite is occurring in neuromyelitis optica spectrum disorder (NMOSD). Disability in NMOSD results from accumulating damage in the CNS related to individual relapses over the course of the disease. Therefore, acute interventions designed to reduce damage may preserve long-term neurologic function.[1,2] The most frequent treatment approach for relapses of NMOSD comprises a schedule of high-dose steroids similar to that adopted in MS, but steroids are only partially effective. Their benefit is most apparent in blunting the extent and severity of the inflammatory response; in fact, only one-third of the patients with NMOSD revert to their previous neurologic status without additional interventions.[3] Escalation to plasmapheresis after steroids in NMOSD relapses leads to a return to baseline in up to two-thirds of the patients.[3]

In this issue of *Neurology: Neuroimmunology & Neuroinflammation*, Dr. Ingo Kleiter and colleagues sought to answer 2 questions about plasmapheresis in acute NMOSD relapses: (1) What type of plasmapheresis is better, plasma exchange (PE) or immunoadsorption (IA)? and (2) what are the clinical factors that predict a good outcome after plasmapheresis?[4]

Plasmapheresis involves the extracorporeal filtration of patients' blood. The simplest form of plasmapheresis is plasma exchange (PE), in which plasma is replaced by synthetic human albumin in saline. PE has been used for numerous inflammatory neurologic disorders.[5] Concerns about bleeding, a rare event caused by the depletion of fibrinogen and other coagulation factors, have prompted the search for novel methods of plasmapheresis. One of these is IA, which implements a protein A column to selectively remove immunoglobulin G (IgG) antibodies while preserving all other plasma proteins and factors. IA has equal efficacy to PE in antibody-mediated conditions, but with fewer bleeding complications.[6]

The authors compared 192 NMOSD attacks that were treated with PE with 38 that were treated with IA. They found that both types of plasmapheresis were equally effective. This suggests that IgG antibody removal is the important treatment effect of plasmapheresis in NMOSD. Although the authors do not compare the bleeding complication rate between PE and IA, it may be inferred that patients with NMOSD would likely have fewer bleeding complications with IA, provided the study was powered sufficiently. However, IA is limited to specialized tertiary care centers and is more expensive. It also carries a risk of reaction to protein A, a cell wall component derived from *Staphylococcus aureus*. The authors answer their first question by conceding that there are not enough data to disentangle the risks and benefits between PE and IA in the acute treatment of NMOSD relapses.

The second question focused on the clinical predictors of a better outcome from plasmapheresis. They found that the use of plasmapheresis (either PE or IA) as first-line therapy and the initiation of plasmapheresis within 3 days of the onset of the attack associated with good outcomes. Forty percent of patients who received plasmapheresis within 3 days returned to baseline compared with less than 4% of those who started plasmapheresis after 7 days. There

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

was still a >80% chance of achieving at least partial benefit for those who started plasmapheresis after 7 days. A third factor that helped predict a favorable outcome with plasmapheresis was aquaporin-4 (AQP4) seropositivity. However, the authors acknowledge that the number of AQP4-seronegative patients was low, thus this part of the study was underpowered. Other studies suggest that AQP4-seronegative patients respond satisfactorily to plasmapheresis for acute relapses as well, implying there may be other autoantibodies at work or other supplementary benefits of plasmapheresis. The final factor predictive of a good outcome with plasmapheresis was the presence of a single lesion, either in the spinal cord or the optic nerve, but not both simultaneously. It is unclear why the latter presentation would not be equally amenable to plasmapheresis.

One of the study items that did not necessarily predict a good outcome was the simultaneous use of disease-modifying immunotherapy at the time of the attack. Disease-modifying immunotherapy not only prevents relapses but seems to reduce the severity of breakthrough episodes.[3] This question remains unanswered.

For acute relapses in NMOSD, the current preferred treatment is plasmapheresis. Unless a patient presents with mild clinical features that reverse quickly with high-dose steroids, the treatment approach of most NMOSD experts is the prompt use of plasmapheresis to limit the inflammatory process and optimize the long-term outcome. Currently, there is no trial design that would allow an unbiased comparison of plasmapheresis vs high-dose steroids alone for relapses of NMOSD. Other potential acute treatments in early phase trials may show promise as well. These include complement inhibitors, as well as intravenous immunoglobulin, especially for myelin oligodendrocyte glycoprotein (MOG)-seropositive NMOSD.[7–9] Whether the combination of these treatments with plasmapheresis may improve outcome is also a question for future studies.

Study funding

No targeted funding reported

Disclosure

M. Levy has served on the scientific advisory boards of Asterias, Chugai, and Alexion; serves on the editorial board of *Multiple Sclerosis and Related Disorders*; holds a patent for Aquaporin-4 sequence that elicits pathogenic T cell response in animal model of neuromyelitis optica and for Use of peptide for diagnostic and therapeutic developments; has been a consultant for Guidepoint Global, Gerson Lehrman Group, and Cowen Group; and has received research support from Viropharma/Shire, Acorda, ApoPharma, Sanofi Genzyme, Alnylam, Alexion, Terumo BCT, NINDS, and the Guthy-Jackson Charitable Foundation. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

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