Plasmapheresis for NMOSD: Not a Rescue Therapy Anymore!?

Neuromyelitis optica spectrum disorder (NMOSD) is a severe autoimmune astrocytopathy with predilection for optic nerves and spinal cord.[1] Unlike multiple sclerosis (MS), attacks of neuromyelitis optica (NMO) are less responsive to pulse steroids.[2] The disability progression in NMOSD is due to cumulative accrual of residual deficits after repeated attacks rather than progressive neurodegeneration as seen in multiple sclerosis.[3] Effective treatment of acute attacks is thus as important as preventing further attacks.

Current approach to the treatment of acute attacks usually consist of giving pulse steroids for 3 to 5 days followed by plasmapheresis if adequate response is not seen.[4] This might result in precious loss of window period for optimal improvement. *In vitro* studies showed that there might be a compensatory stage where the aquaporin-4 channels are internalized after complement and antibody attack.[5] If adequately treated at this stage, the cells might regain their function and avoid necrosis. The corresponding clinical outcome would be complete recovery, which every clinician and patient hopes for. A few cases of Lazarus effect were documented among those patients receiving plasmapheresis on day one in a retrospective study which supports the above notion.[6]

Two large retrospective cohorts which specifically addressed the efficacy and effect of timing of apheresis on clinical outcome concluded that earlier the procedure, better were the outcomes.[6,7] Bonnan and colleagues observed that among 115 attacks of NMOSD, plasmapheresis was done with a median delay of 7 days (0--54). The clinical improvement was complete in 50% of the attacks when plasmapheresis was started at day 0, whereas it was 1--5% when plasmapheresis was started at day 20.[6] Similarly, Kleiter and his colleagues did a retrospective cohort study involving 207 attacks of NMOSD in 105 patients and observed that strong predictors for complete remission were the use of apheresis as first-line therapy and time from onset of attack to start of therapy.[7] Abboud and his colleagues performed a retrospective review of 83 NMO admissions in John Hopkins hospital treated with pulse steroids alone vs pulse steroids along with plasmapheresis.[8] A total of 65% of combination treatment group patients achieved an expanded disability status scale (EDSS) equal or below their baseline at follow-up, while only 35% of the pulse steroids only group patients achieved their baseline EDSS on follow-up. Weinshenker and his colleagues[9] did a randomized controlled trial with a cross over design comparing therapeutic plasma exchange with sham apharesis in 22 patients with inflammatory demyelinating diseases including NMO after a failed trial of pulse steroids. Moderate or greater improvement in neurological disability occurred during 8 of 19 (42.1%) courses of active treatment compared with 1 of 17 (5.9%) courses of sham treatment. In another ambispective study of NMOSD patients presenting with isolated optic neuritis, add on plasmapharesis was associated with higher improvement in visual acquity compared to steroids alone group.[10] Thus, there is substantial evidence that plasmapheresis is effective in treating acute relapses of NMOSD. The timing of plasmapheresis is the latest conundrum, for which the above mentioned studies definitively point toward early initiation.[6-8]

In this issue of Annals of Indian Academy of Neurology, Kumawat and colleagues[11] report a prospective observational study of 30 patients of NMOSD where plasmapheresis was done upfront and as early possible in severe acute attacks of NMOSD, without any glucocorticoids in majority of the patients (21 out of 30 patients). The median time to plasmapheresis was 7 days and outcome was assessed at 3 months. They however excluded patients with longitudinal extensive transverse myelitis (LETM) not meeting diagnostic criteria for NMOSD as well as isolated optic neuritis with aquaporin antibody positivity. They observed that 73.3% of the patients receiving plasmapheresis showed moderate or marked improvement. There was significant correlation between time to initiation of plasmapheresis and percentage improvement in EDSS score. Comparison of those who received pulse steroids and plasmapheresis with those who received only plasmapheresis revealed no significant difference in the percentage improvement of EDSS but there was significant delay in initiation of plasmapheresis in those who received pulse steroids. Also, the presence or absence of aquaporin-4 antibody did not make any difference in the outcome.

Although plasmapheresis seems an effective approach for treatment of acute attacks of NMOSD, how early one should start remains a very critical question? While the evidence points toward "sooner the better," should it bypass steroid use completely? Pragmatically and practically this may be difficult. Steroids are considered standard of care in acute relapses due to ease of availability, decades of experience, lesser need for monitoring, and are expected to have a synergistic effect with plasmapheresis. In practice, patients do respond to steroids alone also. Even in the present study, nine patients were treated with steroids before plasmapheresis was initiated. The outcomes would also be affected by the duration of illness, number of attacks patient has suffered previously, pre-existing disability, and previous immunomodulatory therapy. In the present study too, subjects with longer disease had lesser benefit of plasmapheresis. Also, literature is scarce regarding treatment of relapses with plasmapheresis without steroids. Plasmapharesis also has its concerns for potential complications like hypotension, infection, deep venous thrombosis etc. Thus, combination treatment with steroids and plasmapheresis seems to be the optimal management of

a severe relapse of NMOSD. One of the concerns in giving steroids during plasmapheresis would be their removal from circulation by the procedure. Plasmapheresis usually removes around 1% of the circulating steroids and hence the above concern is not valid and the dose of steroid can always be given after plasmapheresis.[12]

Conclusion

Plasmapheresis is an effective treatment option for acute attacks of NMOSD and probably other acute demyelinating conditions and should be offered to all patients not adequately responding to steroid therapy or upfront in patients with severe attacks irrespective of the site of attack. Although first-line therapy with plasma exchange seems logical and rationale for acute NMOSD and is gaining more acceptability, practical challenges will remain for its widespread use as the first-line treatment. Till such time, a combined therapy with steroids followed by early plasma exchange may seem a practical and balanced approach; please DON'T forget "the earlier the initiation, the maximum is the benefit" and the study by Kumawat and colleagues[10] is a welcome step in this direction for maximizing patient outcome.

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