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Placebo controlled trials in NMO are unethical and not needed YES

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Neuromyelitis optica (NMO) and its spectrum (NMOSD) are rare antibody-mediated autoimmune conditions of the central nervous system (CNS) characterized by recurrent aggressive inflammatory attacks causing demyelination and axonal loss mainly in the spinal cord, optic nerves and other brain areas rich in the water channel aquaporin-4 (AQP4). Recovery from attacks is only partial and the devastating nature of the disease may result in high mortality rate or permanent and severe loss of function such as paralysis, blindness and respiratory failure. In contrast to multiple sclerosis (MS), where disability is dissociated from relapses and accumulates mainly in the later progressive phase of the disease, disability in NMO arises solely from cumulative relapse-related injury. Therefore, effective treatment to prevent relapses and associated disability should be initiated as early as possible.

Most patients, especially those with the relapsing phenotype, are sero-positive for a pathogenic autoantibody directed against AQP4 located on astrocyte foot processes, known also as NMO-IgG. This antibody is highly specific and helps distinguish NMO from MS, where attacks involving the optic nerves and spinal cord are also common.

Immunosuppressive therapies in other rare antibody-mediated autoimmune conditions such as myasthenia gravis and the autoimmune encephalopathies are well-accepted as beneficial although their use is mainly empirical. Standard therapies for these conditions include corticosteroids (CS), plasma exchange (PE), azathioprine (AZA), mycophenolate mofetil (MMF), mitoxantrone or methotrexate (MTX), and their safety profiles are well-

established. It seems unnecessary to reinvent the wheel by performing randomized controlled trials each time a new auto-antibody is identified.

Although all therapeutic studies in NMO to date have been either small, retrospective case series or uncontrolled prospective studies, they have been consistent with supporting a beneficial response of NMO to immunosuppressants including B-cell targeted therapies and established their use as standard of care in NMO. This is reflected in European Guidelines¹ and a consensus document produced by an international group of NMO experts² which support the initiation of preventive treatment with immunosuppressive drugs as soon as the diagnosis of NMO is made. The European guidelines¹ recommend first-line therapy with azathioprine in combination with prednisolone, or rituximab for B-cell depletion, and second line therapy with cyclophosphamide, mitoxantrone or MMF and potentially with MTX or IVIg, with optional PE for treatment escalation. The International Group of NMO Experts² concludes that 6 treatments appear to be likely effective in preventing attacks and stabilizing disability in NMO patients and that the currently available studies provide a limited but helpful insight on treatment effect and tolerability. The expert panel provides recommendations for doses and regimen for 4 first line treatments (azathioprine, MMF, rituximab, or prednisone) and 2 second line treatments (MTX and mitoxantrone), as well as guidelines for monitoring and treatment change considerations. Indeed, several studies have shown that relapses respond to CS and PE, earlier diagnosis and treatment of NMO after the discovery of NMO Ab's resulted in reduction in the mortality rate over the past 20 years, relapses recover better while on immunosuppressive therapy and treatment with AZA+CS or rituximab is associated with a longer time to next attack. Therefore, a standard of care exists for NMO, which is widely accepted. Still, Prospective trials in treatment-naive patients are required to corroborate the efficacy suggested from nonrandomized studies, compare the effectiveness of various regimens to each other, and determine optimal first-line treatment. New potential therapies for NMO need also to be tested in well-designed controlled trials, which may require participation of many centers, and the issue of comparing them to placebo or to one of the recommended first-line therapies is valid for ethical, scientific and clinical reasons.

The rarity of the disease, severity and lack of reversibility of the relapses, early morbidity and mortality in untreated NMOSD suggest that placebo-controlled trials may be unethical. The rationale for comparator rather than placebo-controlled trials may extend beyond the lack of ethics in preventing patient from being treated with recommended therapies, thus exposing them to unnecessary risks of relapses and irreversible neurological damage: The key question about the potential superiority of new agents over the current standard of care will remain unanswered in placebo-controlled trials; Investigators may be under subtle pressures to recruit for a placebo study against their expert opinion and the expected recommendation to start treatment immediately; Recruitment may be slow and insufficient as both clinicians and patients will be reluctant to delay treatment initiation or to take patients off their treatment before enrolling them into the study, and there are likely to be "selection biases", favoring milder patients or those who are unresponsive to standard therapies. Moreover, after study completion, the "better than placebo" and more expensive drug with higher class of evidence but limited safety data may become preferable over currently available effective treatments.

The risk of placebo-controlled trials in NMO can be reduced by shortening the time in the comparative phase, and allowing immediate switch to the active drug after the occurrence of a relapse. However, this may lead to earlier escape from the randomized placebo phase of the study and to insufficient comparative safety data on the new treatment. The claim that total number of relapses required to show a statistically significant difference between the study drug and the placebo is smaller and thus more ethical than when comparing active to current treatment may also be misleading, as this may not be the case if current therapies lack evidence of efficacy (thus providing the ground for "clinical equipoise"), a statement that constitutes the main argument for placebo trials in NMO. Even if it is true and less harm may be caused to the whole group, the risk for the individual patient is greater both in terms of the risk to experience a relapse and the severity of the relapses which have been shown to be milder and recover better with immunosuppressive treatment³.

Although there may be a case for clinical equipoise in NMO and a need for treatments with higher level of evidence and a better benefit/risk ratio, clinical trials in NMO should adopt a design other than a placebo-only control design that is too risky and unethical.

References

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