Myelin oligodendrocyte glycoprotein-IgG (MOG-IgG)-associated disorder (MOGAD) is a recently defined neuroimmunologic disorder affecting the CNS, commonly presenting with acute disseminated encephalomyelitis in children and with optic neuritis and/or myelitis in adults. Although some patients, especially children, may exhibit a monophasic course, there are others who tend to run a highly relapsing course, potentially resulting in long-lasting neurologic disability, akin to those with neuromyelitis optica spectrum disorder (NMOSD). In fact, up to almost half of patients with NMOSD without aquaporin-4 (AQP4-IgG) harbor MOG-IgG. In addition, despite comprehensive testing for aquaporin-4 antibodies, there remains a proportion of patients who phenotypically resemble those with NMOSD but are seronegative for both AQP4-IgG and MOG-IgG.

Recent key phase II and III international, randomized, double-blind, placebo-controlled trials in patients with NMOSD, especially with AQP4-IgG, used drugs with specific immunopathogenic targets and were met with good outcomes in reducing the risk of relapse. Among these was satralizumab, a humanized monoclonal antibody targeting interleukin-6 receptor (IL-6R). The efficacy of satralizumab, as a monotherapy or as add-on therapy, demonstrated the essential role of interleukin-6 (IL-6) in the pathophysiology of NMOSD with contributions toward inflammatory Th17 cell development, production of AQP4-IgG via plasmablasts stimulation, and increased CNS permeability through blood-brain barrier dysfunction. Tocilizumab, another humanized IL-6 receptor inhibitor, emerged as a promising therapeutic option after few case series and a prospective, multicenter, randomized, open label phase II study provided further evidence for NMOSD relapse risk reduction. Similar to satralizumab, most participants in this tocilizumab trial had AQP4-IgG. On the contrary, double-seronegative patients with NMOSD did not seem to respond as well to satralizumab and inebilizumab, with none of these patients included in the eculizumab trial. As for patients with MOGAD, they were either under or unrepresented in these successful studies.

Furthermore, the evidence for efficacy of rituximab, a CD20-mediated B cell-depleting monoclonal antibody, has been less compelling for MOGAD when juxtaposed with AQP4-IgG+ NMOSD. In the prospective observational study by Durozard et al., patients with MOGAD relapsed more frequently (37.5% vs 24%) and earlier (2.6 vs 7 months; median time after last rituximab infusion) as compared to those with AQP4-IgG+ NMOSD. Of note, there were more patients in the MOGAD group who relapsed despite effective B cell depletion while re-emergence of memory B cells was observed in all except 1 of the patients with AQP4-IgG+ NMOSD who relapsed. The lesser effect of rituximab on MOGAD as contrasted with AQP4-IgG+ NMOSD was echoed in another large retrospective multicenter study involving 121 patients. Likewise, a high number of relapses in MOGAD occurred with apparent adequate B cell depletion. The optimal treatment strategy remains unclear in MOGAD, particularly for those with a relapsing course, and in double-seronegative NMOSD.
Consequently, the findings of Ringelstein et al.\textsuperscript{15} published in this issue of *Neurology*: Neuroimmunology and Neuroinflammation are timely and important. In this retrospective, multicenter study, a total of 57 patients with MOGAD, AQP4-IgG+ NMOSD, and seronegative NMOSD had a reduction in median annualized relapse rate (ARR) after receiving tocilizumab for at least 12 months and median treatment duration of 23.8 months. The absence of additional benefit conferred by background therapy further lends support to tocilizumab as a promising monotherapy. All had received various immunotherapies, especially rituximab before treatment initiation with tocilizumab. Equally appealing was the assuring safety profile, which was observed over a span of maximum treatment duration of nearly 9 years.

Retrospective studies are fraught with potential sources of bias inherent to its design. The authors have highlighted some of these including the lack of data homogeneity (e.g., differing treatment and MRI protocols) and availability. The relatively small number of study participants (14 patients with MOGAD, 7 with double-seronegative NMOSD, and 36 with AQP4-IgG+ NMOSD) may also diminish the overall study effect. However, these limitations are not entirely surprising, given the rarity of MOGAD and NMOSD, with or without AQP4-IgG. These limitations should not undo the collective effort and good work by the authors from an international network.

Immunopathogenic mechanisms that are different from those underpinning AQP4-IgG+ NMOSD may, at least in part, contribute to the observed discrepant therapeutic response by MOGAD and double-seronegative patients with NMOSD. Further effort in elucidating the distinct disease mechanisms will shape the appropriate therapeutic recommendations with the main goal to prevent relapse recurrence and hence cumulative neurologic disabilities. Indeed, there have been recent studies demonstrating pathologic features in MOGAD that are different from those occurring in AQP4-IgG+ NMOSD.\textsuperscript{16,17} In the same line of investigations and in our experience, significantly lower levels of CSF glial fibrillary acidic protein levels were detected in double-seronegative patients with NMOSD compared with those with AQP4-IgG during clinical relapses, suggesting a distinct pathophysiology to the established astrocytopathic process of AQP4-IgG+ NMOSD (unpublished).

Positive outcomes as a result of tocilizumab usage, both in efficacy and effectiveness as well as its safety profile, offer a potentially additional treatment option to physicians and patients, either as monotherapy or a switch over from preceding immunotherapies especially in refractory cases. Although the current observation is encouraging, larger confirmatory studies (ideally randomized and controlled) including MOGAD and double-seronegative patients with NMOSD with long-term follow-up are warranted. Nonetheless, Ringelstein et al. have provided us with a platform to build further with this real-world study, involving the largest number of patients with MOGAD to date. Although, in recent years, we have witnessed an expansion of the therapeutic landscape for AQP4-IgG+ NMOSD patients, these findings continue to lend a hand in demystifying MOGAD and double-seronegative NMOSD.

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**References**

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