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Immunotherapy in Double Negative NMOSD: A Scoping Review

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INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) are chronic autoimmune inflammatory diseases of the central nervous system, characterized by severe relapsing episodes of optic neuritis and longitudinally extensive transverse myelitis. Most patients are seropositive for AQP4 antibodies, while seronegative patients may either be seropositive for myelin oligodendrocyte glycoprotein (MOG) or have no detectable antibodies. In our study, This study aims to explore, review, and assess various **treatment** options for this specific population, referred to as **double negative NMOSD (DN NMOSD)**

METHODS

A scoping review was conducted following **PRISMA-ScR** guidelines. From 3,256 articles identified in PubMed, Embase, Cochrane, Scopus, and Web of Science, **22 studies** met the inclusion criteria. A data charting strategy was developed to extract variables such as author, year, study type, number of DN NMOSD patients, patient age, disease duration, and immunotherapy details. Corticosteroids, mycophenolate mofetil, intravenous immunoglobulin (IVIG), plasma exchange (PE), tryptophan immunoadsorption (Tr-IA), azathioprine, and monoclonal antibodies were analyzed separately to assess their efficacy in double seronegative patients.

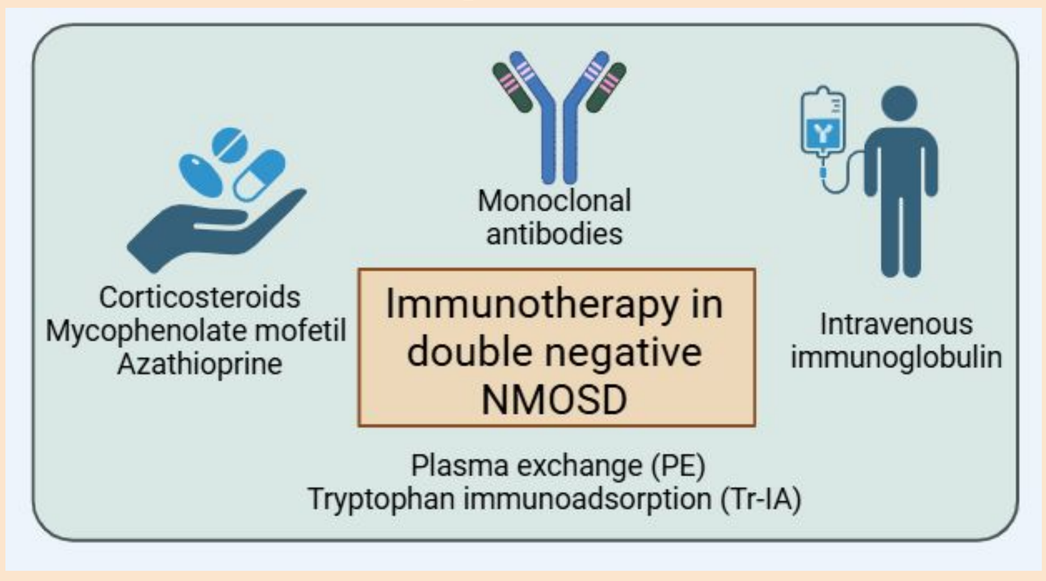
Figure 1. Databases used to search for articles on the topic, with a total of 22 studies included.

RESULTS

Corticosteroid therapy was effective in AQP4+ patients but had limitations in those negative for AQP4 and MOG antibodies. The combination of plasma exchange early significantly improved outcomes. Mycophenolate mofetil (MMF) demonstrated efficacy in AQP4+ patients, reducing relapse rates, instability, and disability. However, in double-negative patients, responses varied, with benefits observed in some cases. The drug's teratogenicity requires contraception in women of reproductive age.

IVIG in AQP4+ patients improved visual recovery and disability, especially when combined with steroids, but responses in double-negative patients were less predictable. Thus, IVIG is considered a second-line option for those unresponsive to steroids or other therapies, particularly in AQP4+ patients. PE showed positive responses in all seronegative patients; however, only half had undergone anti-MOG testing. Regarding Tr-IA, two patients responded to both induction and maintenance therapy -one experienced greater stabilization and improved visual function, while the other improved ambulation with no adverse effects - making it a promising and well-tolerated option. Azathioprine has shown promise in managing for NMOSD treatment, contributing to disease stabilization and neurological function improvement.Among monoclonal antibodies, rituximab was the most studied, showing improvements in relapse rates and disability scores. However, double-seronegative patients exhibited a higher risk of disease reactivation after rituximab dose reduction. With inebilizumab, double-seronegative patients experienced attacks without a corresponding increase in serum GFAP levels. Tocilizumab reduced relapse risk in both seropositive and seronegative patients, while satralizumab has shown no benefit in seronegative cases.

Figure 2. Different modalities of immunotherapy in double negative NMOSD patients



CONCLUSION

This study highlights the limited and **emerging literature on immunotherapy in DN NMOSD patients.** Establishing well-defined treatment strategies and management approaches requires conducting both randomized and non-randomized clinical trials to strengthen the existing evidence. Furthermore, ensuring the availability of anti-MOG and anti-AQP4 testing is essential for research centers to accurately identify target patient populations.

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