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**Letter to Editor**

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# Eculizumab in the treatment of neuromyelitis optica spectrum disorder

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Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune and demyelinating disease of the central nervous system (CNS) characterized by unpredictable attacks of optic neuritis (ON) and myelitis which often leads to paralysis and visual loss. For a long time, it was known as one of the multiple sclerosis (MS) variants, but after the discovery of neuromyelitis optica (NMO)-associated immunoglobulin G (IgG) antibody which targets the water channel membrane protein aquaporin-4 (AQP4), it was considered as a separate clinical entity.[1]

Early and aggressive treatments are critical in NMOSD due to relapses and consequent severe disability. The objective of these treatments is reducing CNS damage, improving neurological functions, and importantly suppressing inflammatory attacks.[2] Conventional immunosuppressive therapies for NMOSD have been used out of license and their off-label use is only supported by uncontrolled observational studies and their effectiveness in other antibody-mediated disorders.[3] Moreover, 33% to 75% of patients who received these agents experience relapse again which shows the urgent need for additional treatments with identified results.[4]

Antibodies against AQP4, a water channel of CNS astrocytes, are expressed in nearly 65% to 90% of patients with NMOSD. Preclinical findings demonstrated that AQP4 antibodies acted as an activator exciting inflammation and formation of membrane attack complex which causes astrocytes destruction and neuronal damage.[5,6] Eculizumab is a humanized monoclonal antibody that targets terminal complement protein C5 and reduces the risk of relapse in AQP4-IgG-positive patients and is the first approved drug for the treatment of NMOSD.[7] Recently in the United States of America (USA), Canada, European Union (EU), and Japan, eculizumab was approved for adults with AQP4-IgG-seropositive NMOSD.[3]

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To review existing literature describing the effectiveness of eculizumab on NMOSD, we carried out a research. We searched PubMed, Scopus, and Web of Science to identify relevant studies. The original investigation which described the effect of eculizumab on patients with NMOSD was considered eligible. After the two steps of abstract and full-text screening, the following data were extracted from included studies: study identifier (ID), publication, region, study design, sample size, mean age, number of male participants, number of a placebo, baseline Expanded Disability Status Scale (EDSS) score, EDSS score after treatment, AQP4-IgG status, eculizumab dosage, treatments before eculizumab receiving, treatments after eculizumab discontinuation, main findings, baseline characteristics of patients, and adverse events. Our literature search yielded 185 papers that were reviewed and three studies with overall 158 cases by the mean age of 43.9 (Table 1). Among them, 96 received eculizumab. Only one of the papers had a randomized design,[7] and the two remaining studies each were open-label trial[8] and case report.[9] According to included studies, patients experienced approximately 2 to 4 relapses per year before eculizumab receiving with a mean EDSS score of 4. Moreover, only one of the patients was AQP4-IgG-negative (Table 1). In a randomized controlled trial (RCT) by Pittock et al.[7] and a case report by Digala et al.,[9] 900 mg eculizumab every week for the first month, and then 1200 mg every two weeks was administered, while in the third study, the eculizumab dosage was lower (600 mg weekly first month, and then 900 mg every two weeks).[8] Based on the included studies, number of relapses were significantly decreased after eculizumab intake. In Pittock et al. study, 12 of 14 patients did not experience attack during 12 months of eculizumab treatment,[8] and the other study by the same author with a larger sample size revealed that relapses occurred in 3 of 96 patients (3%) in the eculizumab group and 20 of 47 (43%) in placebo group.[7] Furthermore, one of the cases from a case report remained relapse-free after one year of receiving eculizumab.[9] Besides, visual acuity improved in five patients in one of the studies, while other studies did not report the visual acuity status after treatment.[8]

According to the results, the EDSS score was improved by 0.27 due to eculizumab intake among all patients who received eculizumab. In the RCT study, the mean change of EDSS score was 0.18 in the eculizumab group and 0.12 in the placebo group which is not significant.[7] In contrast, the other studies demonstrated that the patient's disability status was significantly improved.[8,9] Several side effects were reported including headache, meningococcal sepsis, and rheumatoid arthritis which the headache was the most common.[7,8] In addition, a higher number of upper respiratory tract infections and headaches were observed in the eculizumab group compared to controls in the Pittock et al. investigation, and also there was one death due to pulmonary empyema in a patient who received eculizumab.[7] No side effects were reported in the case of the Digala et al. study[9] (Table 1).

The complement system (complement cascade) is a part of the immune system which is also involved in the final pathway of inflammation in autoimmune diseases such as MS and NMOSD.[1] Nowadays, there are lots of efforts to develop drugs that affect multiple constituents of the complement system. Eculizumab is one of these drugs which binds to the terminal complement component C5 with a high affinity to inhibit its cleavage to C5a and C5b. C5a is a pro-inflammatory mediator, and C5b leads to producing of the membrane attack complex C5b-9.[10] The pathophysiologic mechanism of eculizumab in the treatment of NMOSD is shown in figure 1.

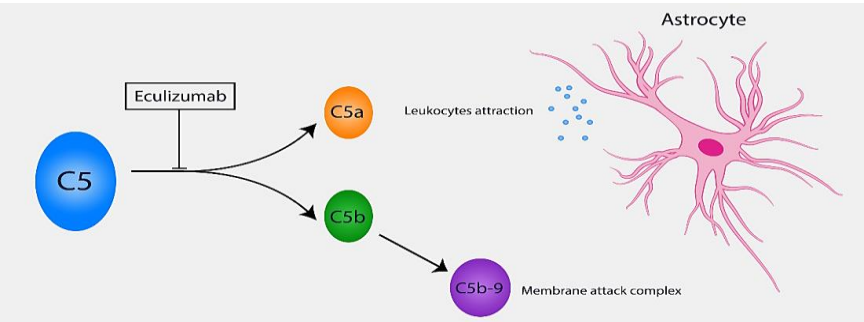


**Figure 1.** Pathophysiologic mechanisms of complement system in neuromyelitis optica spectrum disorder (NMOSD) and effect of eculizumab. Eculizumab binds to C5 and inhibits its cleavage to C5a and C5b and consequent leukocytes attraction and formation of membrane attack complex C5b-9

**Table 1.** Demographic, clinical characteristics and findings of included studies (part I)

| Study | Publication | Region | Study design | Sample size | Mean age (year) | Men | Placebo (n) | Baseline EDSS score | EDSS score after treatment | AQP4 IgG status | Eculizumab dosage |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Digala et al.[9] | Frontiers in Neurology | USA | Case report | 1 | 35.0 | 0 | 0 | 4.0 | 2.0 | Seronegative | 900 mg weekly first month, and then 1200 mg every two weeks |
| Pittock et al.[8] | Lancet Neurology | USA | Open-label trial | 14 | 41.1 | 0 | 0 | 4.3 | 3.5 | Positive | 600 mg weekly first month, and then 900 mg every two weeks |
| Pittock et al.[7] | The New England Journal of Medicine | 18 countries | Randomized double-blind clinical trial | 143 | 44.3 | 52 | 47 | 4.0 | 3.8 | Positive | 900 mg weekly first month, and then 1200 mg every two weeks |

EDSS: Expanded Disability Status Scale; AQP4: Aquaporin-4; IgG: Immunoglobulin G

**Table 1.** Demographic, clinical characteristics and findings of included studies (part II)

| Study | Treatments before eculizumab receiving | Treatments after eculizumab discontinuation | Main findings | Baseline characteristics | Adverse events |
|---|---|---|---|---|---|
| Digala et al.[9] | Intravenous methylprednisolone, PLEX, rituximab, mycophenolate mofeti, oral prednisone | Naïve | EDSS score was reduced by approximately 2, no relapses or adverse events, and patient remained relapse-free and symptom-free after drug discontinuation | 4-5 relapses per year, lower limb weakness, MRI and visual evoked potential were normal, IgG index and oligoclonal bands were normal | No adverse events |
| Pittock et al.[8] | Mycophenolate mofetil (n = 5), prednisone (n = 2), azathioprine (n = 7), rituximab (n = 4) | Azathioprine, prednisone, rituximab, mycophenolate mofetil, intravenous methylprednisolone | EDSS score was reduced by mean of 0.8, visual acuity improved in five patients, AQP4-IgG titers remained unchanged until eculizumab discontinuation, 12 patients had no attacks | In the year preceding enrolment, 39 attacks were reported in all patients ranging from two to four for each patient | Headache, meningococcal sepsis, rheumatoid arthritis |
| Pittock et al.[7] | Rituximab (n = 46), azathioprine (n = 50), mycophenolate mofetil (n = 25), glucocorticoids alone (n = 27) | None | Relapses occurred in 3 of 96 patients (3%) in the eculizumab group and 20 of 47 (43%) in the placebo group, no significant difference between groups in EDSS change | Annualized relapse rate was 1.99 | Higher number of upper respiratory tract infection and headache in the eculizumab group, one patient who received eculizumab died from pulmonary empyema |

EDSS: Expanded Disability Status Scale; AQP4: Aquaporin-4; IgG: Immunoglobulin G; MRI: Magnetic resonance imaging; PLEX: Plasma exchange

In conclusion, our review showed that eculizumab might have promising results in the treatment of NMOSD especially in terms of reducing relapses. In addition, the EDSS score was decreased due to eculizumab treatment but not significantly. Eculizumab showed promising results regarding efficacy and safety in NMOSD AQP4-IgG-positive patients. Moreover, eculizumab may be beneficial for AQP4-IgG-seronegative patients, but the data were limited. However, due to the limited number of evidence, further investigations with randomized design, longer follow-up, and larger sample sizes are strongly needed to identify the therapeutic effect of eculizumab on NMOSD. Further, clarifying the exact mechanism of eculizumab action in NMOSD warrants further investigations.

## Conflict of Interests

The authors declare no conflict of interest in this study.

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