

Efficacy and safety of rituximab in neuromyelitis optica: Review of evidence

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Neuromyelitis optica (NMO) is an autoimmune inflammatory disease of the central nervous system with preferential involvement in the optic nerve and spinal cord with a widespread spectrum of clinical features; multiple therapeutic agents have been used with different results. Recent evidence points to B-cell-mediated humoral immunity in the pathogenesis of NMO. Rituximab targets the CD20 antigen on B-cells. Treatment leads to profound B-cell depletion, principally over an antibody-dependent cell cytotoxicity mechanism. The aim of our study was to review clinical trials to elucidate the impact of rituximab on the relapse rate, Expanded Disability Status Scale (EDSS), and progression of disability in NMO. We performed a comprehensive review of all studies that evaluated clinical and paraclinical effects of rituximab on NMO. MEDLINE-PubMed, Web of Sciences, EMBASE, and Cochrane databases up to June 2016 included in our searches. In addition, reference lists from articles identified by search as well as a key review article to identify additional articles included in the study. Rituximab targets the CD20 antigen on B-cells and decreases attack frequency and severity in patients with NMO; however, it does not remove attacks, even when modifying treatment to achieve B-cell depletion. Most of the investigations revealed that EDSS significantly in all patients with rituximab treatment will be decreased after treatment with rituximab. No new or enlarged lesions or pathological gadolinium enhancement was observed in serial brain and spinal cord magnetic resonance imaging, except for those observed concomitantly with clinical relapses and the median length of spinal cord lesions was significantly reduced after therapy. Rituximab targets the CD20 antigen and decreases attack frequency and severity in patients with NMO.

Key words: CD20 antibody, neuromyelitis optica, rituximab

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INTRODUCTION

Neuromyelitis optica (NMO) is a severe autoimmune disorder of the central nervous system (CNS) which is predisposed to the optic nerves and spinal cord. Traditionally, neurologists, particularly in Asian nations, believed NMO to be a subtype of multiple sclerosis (MS), whereas others considered it a distinct disease.^[1] NMO, similar to various other autoimmune disorders, is predominant in women (4:1–9:1 in most studies).^[2] The median age of onset is 30–40 years, but adults older than 65 years and children may also be affected.^[3]

A major development was the discovery that most patients with NMO have detectable serum antibodies that target the water channel aquaporin-4 ([AQP4]-immunoglobulin G [IgG]), are highly specific for clinically diagnosed NMO, and have pathogenic potential. Despite the use of sensitive evaluates, AQP4-specific antibodies are not found in 10%–40% of patients diagnosed with NMO or NMO spectrum disorders (NMOSDs).^[4] For this purpose, anti-myelin oligodendrocyte glycoprotein antibodies have been identified in several patients with clinical features of NMOSD, but who are lacking anti-AQP4 antibodies.^[5] A widespread spectrum of clinical features, consisting of recurrent optic neuritis (ON), longitudinally extensive transverse myelitis (LETM), and some encephalitic

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presentations, are renowned as the spectrum is referred to as NMOSD.

A majority of the patients with NMO experience a relapsing progressive course resulting in disability. Multiple therapeutic agents have been used with different results. Recent evidence points to B-cell-mediated humoral immunity in the pathogenesis of NMO. The CD20 molecule is a transmembrane protein expressed on a broad range of cells of the human B-cell lineage, from pre-B-cells through naive and memory B-cells. Rituximab (Rituxan, Genentech and Biogen Idec, RTX) signifies the first genetically engineered chimeric anti-CD20 monoclonal antibody (mAb) that was found to target and proficiently reduce circulating CD20+ B-cells in humans.

A developing concentration in the potential benefits of targeting B-cells in nonneoplastic disorders has led to clinical trials of rituximab in several peripheral and CNS disorders including MS and NMO. However, its definite efficacy and safety have not yet been clarified. The aim of our study was to review clinical trials to elucidate the impact of rituximab on the relapse rate, magnetic resonance imaging (MRI) findings, Expanded Disability Status Scale (EDSS), and progression of disability in NMO.

METHODS

Two of us (ME and MS) independently searched the MEDLINE, Central Register of Controlled Trials, and clinicaltrials.gov databases (published between January 1, 2000, and July 31, 2015) using the terms NMO, rituximab, Devic's disease, and mAb. A comprehensive literature search was performed by two authors with expertise in neurology, clinical epidemiology, and systematic review methodology. Review articles and references of all papers were overviewed for potentially relevant studies.

Inclusion criteria

The following criteria were used to include studies

- NMO was defined according to accepted international diagnostic criteria
- Efficiency and tolerability of MS were calculated
- Papers were published in English.

After removing duplicate data, abstracts, and in some cases, full text of paper, were screened by two reviewers independently to assess the eligibility of the study to be included in our study. All potentially eligible studies were reviewed independently by the two trained reviewers (OM and EF). Any discrepancies following full article review were solved by a third reviewer (MS). Extracted data were verified by another reviewer (RN).

We performed a comprehensive review of all studies that evaluated clinical and paraclinical effects of rituximab on NMO. MEDLINE-PubMed, Web of Sciences, EMBASE, and Cochrane databases up to June 2016 included in our searches. In addition, reference lists from articles identified by search as well as a key review article to identify additional articles included in the study.

NEUROMYELITIS OPTICA

NMO is an autoimmune inflammatory disease of the CNS with preferential involvement in the optic nerve and spinal cord. NMO was first diagnosed in the 19th century and was long considered a clinical alternative to MS. NMO is concomitant with autoantibodies to the water channel AQP4 expressed on astrocytes.^[6] AQP4 led researchers to consider the role of humoral immunity in NMO pathology.^[7] After crossing the blood-brain barrier, memory B-cells are restimulated in the CNS and after clonal expansion, differentiate into antibody-secreting plasma cells.^[8] In 2007, the term NMOSD was presented to include high-risk patients with restricted or initial forms of NMO (e.g., first-attack LETM or recurrent or bilateral ON), who were seropositive for AQP4-IgG. It also included AQP4-IgG-seropositive patients with concomitant autoimmune disorders. The term NMOSD also contained the cerebral, diencephalic, and brainstem lesions that occur in a minority of patients with typical NMO. Finally, NMOSD potentially included patients diagnosed with opticospinal MS; an MS phenotype prominent in Asia and distinguished from Western MS. The course of the disease is commonly manifested in relapses, and the quick disability it produces is associated with high rates of early mortality. Its prevalence is assessed to range from <1–4.4/100,000 in the West. More women than men have NMO (ratio 9:1 compared with 2:1 in MS). The median age of onset, 39 years, is almost 10 years higher than that in MS.^[9] The core clinical features of NMO contain ON, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, and symptomatic cerebral syndrome with NMOSD-typical brain lesions. Because no characteristic is pathognomonic, clinical judgment remains essential. According to the criteria proposed by Wingerchuk *et al.*,^[10] MRI lesion patterns are a key point facilitating CNS demyelinating disease differential diagnosis. Neuroimaging characteristics of NMOSD include several patterns are characteristic or highly suggestive of NMOSD, involving the brain (lesions involving the dorsal medulla, hypothalamus, fourth ventricle, and corpus callosum), optic nerve (unilateral or bilateral increased T2 signal or T1 gadolinium enhancement within optic nerve or optic chiasm), and spinal cord (LETM, central cord predominance, and gadolinium enhancement of the lesion

on T1-weighted sequences). A diagnosis of NMO can be made based on AQP-IgG availability. If AQP-IgG status is accessible, the diagnostic criteria include (1) at least one core clinical characteristic, (2) positive test for AQP4-IgG, and (3) exclusion of alternative diagnoses. If serologic testing is unavailable, diagnostic criteria for NMOSD comprise at least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements: (a) at least one core clinical characteristic must be ON, acute myelitis with LETM, or area postrema syndrome; (b) dissemination in space (two or more different core clinical characteristics); (c) fulfillment of additional MRI requirements as applicable; (d) negative tests for AQP4-IgG using best-available detection method or testing unavailable; and (e) exclusion of alternative diagnosis.

A profitable treatment for NMO does not exist to date. Instead, the key management aims are as follows: (1) improvement of relapse-associated symptoms; (2) symptomatic therapy of residual symptoms; and (3) long-term stabilization of disease progression. In the case of a definite diagnosis of NMO, depending on severity of the attack, an oral steroid tapering period should be considered. Because NMO takes a relapsing course in most cases, with often imperfect recovery and rapid accumulation of neurological deficits, long-term immunosuppressive treatment should be initiated when the diagnosis of NMO has been established.

TREATMENT OF NEUROMYELITIS OPTICA

Acute treatment

Building on decades of experience using corticosteroids to treat inflammatory relapses in MS and other inflammatory disorders, high-dose intravenous methylprednisolone was extensively adopted as a first-line agent to broadly suppress inflammation in acute NMOSD relapses. Permanent injury from relapses in NMO leads to aggregate disability. Therefore, the consensus among experts in NMOSD is that every relapse needs to be treated and high-dose corticosteroids are good starting agents. The typical initial dose for the treatment of NMOSD is 1000 mg of methylprednisolone intravenously for 5 days, ordinarily monitored by an oral steroid taper for 2–8 weeks depending on the severity of the attack. The initial aim for corticosteroid use in acute NMOSD relapses is to decrease the edema and secondary inflammation in the lesion. If there is minimal or no improvement with high-dose corticosteroids based on the clinical judgment of a physician, the use of plasma exchange (PLEX) has been shown to be beneficial in NMOSD. Additional studies since have recommended that PLEX following a course of high-dose steroids is more effective than corticosteroids alone in attaining preattack neurological function.^[11] Intravenous immunoglobulin (IVIg) has been used extensively for

treatment of various neuroimmunological disorders,^[12] but its role in inflammatory disease of the CNS is less clear. Of one series of ten patients with NMOSD unresponsive to corticosteroids ± PLEX, IVIg was helpful in five.^[13]

Preventive treatment

Immunosuppression with steroid-sparing agents is the backbone of treatment. Azathioprine, mycophenolate mofetil, and rituximab are the most broadly used first-line agents although methotrexate, cyclosporine, tacrolimus, and cyclophosphamide can also be prescribed. NMOSD patients with positive AQP4-Ab are particularly steroid dependent.

Symptomatic treatment

Symptomatic treatment of immobility, neuropathic pain, spasticity, urinary retention/incontinence, depression, fatigue, and cognitive dysfunction in NMOSD patients has not been sufficiently studied.^[14] First-line agents that have been most effective in treatment of both neuropathic and spastic pain are antiepileptic medications. Gabapentin dosing is usually started at 300 mg three times daily and titrated up, as needed weekly, to a maximum dose of 2400 mg/day. Carbamazepine at 100–200 mg twice daily is also predominantly effective at treating both neuropathic and spastic pain in NMO. There are two options for patients with urinary retention. The most widely recommended option is intermittent self-catheterization at least three times daily or more often, depending on bladder volumes throughout the day. The second option is bethanechol at a dose of 25 mg three or four times daily that increases bladder muscle tone and contraction.^[15] NMOSD patients can have sleep disorders such as those secondary to nocturia, chronic pain, and obstructive sleep apnea. Sleep disorders not only lead to fatigue but also influence a patient's recovery potential and overall neurological comfort.^[16]

THE ROLE OF B-CELLS IN THE PATHOGENESIS OF NEUROMYELITIS OPTICA

B-cells can perform a widespread array of normal roles that, when dysregulated, may cause NMO disease activity: antigen presentation, pro-inflammatory and anti-inflammatory cytokine construction, and immunoglobulin production. While the role of B-cells in autoimmune disorders may alter during different phases of the disease, the apparent ability of B-cell reduction to limit new NMO disease activity indicates an overall pro-inflammatory role for B-cells in NMO, probably due to altered numbers or abnormal activity of pro-inflammatory or regulatory B-cell subdivisions.^[7] Potential mechanisms comprise development of AQP4-specific plasmablast clones, failure to abolish autoreactive B-cell subsets, inadequate antigen-specific regulatory B-cells, and the loss of anergic maintenance.^[17] B-cell tolerance

deficiencies have been obviously demonstrated in a number of autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, and Type 1 diabetes. This autoreactive B-cell reservoir is believed to be the pool from which disease-associated autoantibodies are insulated. Dysfunctional B-cell tolerance may contribute to the production of AQP4-IgG and other autoreactive peripheral B-cells. Since disease activity is related to the production of AQP4 autoantibody in the majority of the patients with NMO, regulation of central and peripheral B-cell checkpoints may directly slow down disease activity. Human B10 regulatory B-cells may play an important role in suppressing AQP4-specific and innate, immune responses in NMO.^[18]

RITUXIMAB

Rituximab is a chimeric mAb made up of a human IgG1 with variable regions from a murine anti-CD20 clone. CD20 is a marker of B-cell lineage that is progressively expressed on the outer membrane from pre-B-cell stage to the memory B-cell stage.^[19] Rituximab targets the CD20 antigen on B-cells. Treatment leads to profound B-cell depletion, principally over an antibody-dependent cell cytotoxicity mechanism. It was primarily designed for use in non-Hodgkin lymphoma but has consequently been established to be advantageous in the treatment of autoimmune rheumatologic and neurological disorders including NMO. Rituximab is thought to decrease attack frequency and severity in patients with NMO; however, it does not remove attacks, even when modifying treatment to achieve B-cell depletion.^[20] Plasmablasts do not express the CD20 antigen and are not depleted following rituximab treatment. They can be recognized using the CD19 surface antigen marker. Persistence of NMO IgG-producing plasmablasts may elucidate some of the variability in clinical response.^[21]

EFFECT OF RITUXIMAB ON THE LEVEL OF CD19/CD20

Rituximab exerts its function through two stages. In the first stage, all CD19+ B-cells, whether regulatory or pro-inflammatory, are deleted. T-B-cell interaction is interrupted and the number of autoantibody-producing plasma cells as precursors declines sharply. In the second stage, B-cells begin to appear again in the peripheral blood and repopulate. However, the composition of the repopulated B-cells is changed and the ratio of memory and regulatory B-cells is reserved. The dominance of pathogenic memory B-cells before rituximab treatment turns into the dominance of protective regulatory B-cells after treatment, leading to a more suppressive or tolerogenic immune context. Altogether, rituximab induces early benefit by eliminating or inhibiting pathogenic effector

B-cells, whereas delayed and more sustained improvement depends on the preferential expansion of B-cells with regulatory functions.^[21,22] Quan *et al.* explore the impacts of high-dose methylprednisolone therapy and rituximab on circulating B-cells in 22 NMO patients. One infusion of 100 mg on the 1st day; if there are no allergies or other adverse reactions in day 1, another infusion of 500 mg was given on day 2. The main finding of the current study is that, first, the quantity and function of Breg were significantly impaired in NMO patients in acute relapse phase before treatment.^[18] At a mean follow-up time of 48 months on 21 Caucasian patients affected by NMO and NMOSD, who underwent at least one cycle of intravenous treatment, Radaelli *et al.* confirmed that rituximab is effective and safe in Caucasian NMOSD patients. Rituximab infusion induced a complete suppression of CD19 + B lymphocytes after 1 month in all patients. This effect lasted for at least 5 months; during month 6, the level of CD19 + B-cells began to rise. A long-lasting effect of rituximab was observed in patients showing concomitant leukopenia. To prevent disease reactivation due to a delayed treatment, Radaelli *et al.* decided to repeat rituximab infusion every 6–7 months, even in the absence of CD19+ B-cell detection. From the third course, they used a single infusion of 1000 mg per course, obtaining a complete suppression of CD19+ B-cells that lasted at least 6 months, and a control of the disease that was comparable with previous studies using a higher dosage of rituximab. A prolonged effect of rituximab on CD19+ B-cells was observed in patients with concomitant persistent leukopenia. Yang *et al.* treated five Chinese patients with deteriorating NMO and NMOSD with a 100 mg IV infusion of rituximab once a week for 3 consecutive weeks. The regimen of rituximab was sufficient to reduce total CD19 B-cells, as well as the memory component of CD19CD27 B-cells, in all five patients with NMO. At week 53 after initial infusion, CD19 B-cell counts were still 1% in one patient, whose CD19CD27 B-cell counts were 0.05%.^[23]

EFFECT OF RITUXIMAB ON PATIENT'S EXPANDED DISABILITY STATUS SCALE

Mean EDSS scores were reportedly decreased in 13 of the studies. One study reported an increase in mean EDSS score after RTX therapy.^[24] Different values such as worsened, improved, and stabilized EDSS scores were available for another study, showing relatively more establishments and improvements rather than worsened states after RTX therapy in the patients.^[25] de Andrés *et al.* reported a decreased mean EDSS score from 9 to 6.5, which was at the point, the patient had improved and was able to walk short distances with crutches.^[21] The study of Collongues *et al.* contained 21 patients with mean EDSS of five reduced

to three after therapy.^[26] Kim *et al.* reported a decrease from a 4.4 median EDSS score before RTX therapy to 3 after therapy in their study. EDSS scores improved in 24 patients, stabilized in 5, and worsened by 0.5 points in one patient.^[27] Zéphir *et al.* conducted a cohort study and reported a mean EDSS score of 5.8 ± 2.4 before therapy, and a significant decrease in mean EDSS after therapy of 3.9 ± 2.6 . They also mentioned that the variations of EDSS scores were not significantly reduced in both groups, and the EDSS scores were significantly reduced after rituximab therapy.^[28] In the study by Fernández-Megía *et al.*, mean EDSS decreased from 4 to 3.25 after RTX therapy including three stable and three improved scores out of six patients.^[29] Kim *et al.* conducted a retrospective review of 100 patients to evaluate the treatment outcomes of RTX in NMO patients. In their study, the median EDSS score was four before rituximab treatment and three after treatment. The EDSS scores improved in 58 patients and stabilized in 38 patients.^[30] A decrease from 4.5 to 4 in mean EDSS score before RTX therapy in comparison to the score after therapy is reported in the study by Yang *et al.* Three of their patients presented with a tendency of EDSS scores reduction, whereas two experienced no changes. They mentioned that although some of EDSS score reductions did not achieve statistical significance, patients experienced significant improvements overall in pyramidal, sensory, and bowel functions after therapy.^[23] In a study conducted by Kim *et al.*, out of thirty patients, the EDSS scores improved in 24 patients and stabilized in four. The median EDSS score was 4.0 (range 1.0–8.5) before rituximab treatment and 3.0 (range 1.0–7.5) after treatment. Worsening of the EDSS score after rituximab was observed in only four patients.^[31] Graves *et al.* evaluated a total of 114 patients with different types of MS and NMO, of which only 16 had NMO. A total of 42 EDSS scores were available from both MS and NMO patients with baseline mean EDSS score 6. In 11 of 42 patients with multiple cycles of RTX, postinfusion EDSS scores showed four stable EDSS scores, three exhibitions of worsened EDSS scores after each cycle, four improved scores after the first cycle, and stable scores after each subsequent cycle. Of the remaining 31 patients who received a single cycle, 9 appearances of worsening EDSS scores, 9 improved, and 13 stable EDSS scores were reported.^[25] Lindsey *et al.* reported five worsened mean EDSS scores, one stable and four improved EDSS scores in a total of 10 patients in their study, demonstrating an increase from 3.65 before RTX therapy to 5.2 after RTX therapy.^[24]

EFFECT OF RITUXIMAB ON RELAPSES OF NEUROMYELITIS OPTICA PATIENTS

In 2013, out of thirty patients, 60% were completely free from relapse over 5 years. In 2011, of thirty patients, 28 showed a marked reduction in relapse rate by 88%

and 70% of patients became relapse-free over 24 months. Five of 25 patients studied by Kim *et al.* had a relapse after rituximab induction. A similar relapse rate within 3 months of rituximab was recorded by Javed *et al.*; Lindsey *et al.* noted that three of nine patients relapsed within 1 month of rituximab, and one patient relapsed during the immediate postrituximab period on three separate occasions. Ayzenberg *et al.* reported two patients with NMO who had a relapse within days of RTX infusion and who were then successfully treated with tocilizumab. Severe relapses within 1 month of RTX were also documented by Capobiano *et al.* and Sanchez-Carteyron *et al.* In addition, none of the 23 patients with NMO in the series of Bedi *et al.* experienced a postrituximab relapse. In one study performed by Jai S. Perumal *et al.*, six of 17 (43%) patients with NMO who received >1 dose of rituximab experienced a relapse within 1 week of their first rituximab infusion.

IMPACT OF RITUXIMAB ON PATIENTS' MAGNETIC RESONANCE IMAGING

MRI plays an important role in diagnosis, prognosis, and choosing the distinct treatments of NMO and NMOSD from CNS inflammatory diseases. Imaging findings before and after rituximab therapy have been reported in some studies.^[21,32] Generally, it gives the impression that MRI findings suggest no new, active, or extended lesions after the treatment with rituximab^[33] although worsening of symptoms along with enhancing injuries has also been reported.^[34] de Andrés *et al.* studied a 17-year-old patient affected by NMO. Results from a brain MRI scan after treatment with rituximab and IVIg, including an optic nerve study, were reported to be normal. Continuous spinal cord thinning from C1 to T10 with no gadolinium uptake was demonstrated by the spinal cord MRI scan.^[21] Radiologic progression with no clinical relapse resulted in mycophenolate mofetil increases after rituximab initiation, as reported in another study by Beres *et al.* At 6 months after the first course of RTX therapy in the 20-year-old female, the patient experienced a new mild spinal cord relapse confirmed by the presence of a new MRI enhancing lesion in the cervical spine. At 6 months after the second course of rituximab, the patient was reported to be in a stable condition, scoring EDSS 1.0 and no new MRI lesions or activity had been detected. Longoni *et al.* assessed five patients clinically and radiologically at onset, 1 and 3 months from onset, every 6 months thereafter, and at the time of suspected clinical relapses. It has been reported that no patient demonstrated any further extension of brain or spine lesions after rituximab-induced B-cell depletion. Radaelli *et al.* studied long-term safety and efficacy of rituximab therapy on 21 patients affected by NMO. Brain and spinal cord MRI was performed every 6 months or in the presence of new clinical symptoms. Finally, no new or

enlarged lesions or pathological gadolinium enhancement were observed in serial brain and spinal cord MRIs, except for those observed concomitantly with clinical relapses. Yang *et al.* studied five patients with deteriorating NMO and NMOSD treated with rituximab. Lesion segments of the spinal cord before treatment with rituximab were reported 8, 7.5, 4, 1, and 6, respectively, in five patients, which decreased to 3.5, 1, 1, 0.5, and 5 after treatment. MRI assessment demonstrated no new T2 lesions and no enhancement in the CNS in all five patients treated with rituximab during the 1-year follow-up period.^[35] The median of total T2 lesions in brain and spinal cord before and after rituximab therapy was 3 and 2.5, respectively. The median length of spinal cord lesions before and after therapy was 5 and 2.5 vertebral segments, respectively, which was significantly reduced over the 1-year period.^[23]

SAFETY OF RITUXIMAB

Almost all of the studies reported some adverse effects in rituximab therapy for NMO patients. Some of these effects were related to drug infusion and most of them were nearly transient. As an example in a trial performed by Fernández-Megía *et al.*, two patients presented some types of infusion-related adverse effect after the first dose of rituximab that was resolved with administration of 80 mg methylprednisolone and an antihistamine.^[29] In another study that was performed by Radaelli *et al.*, serious infectious status due to rituximab therapy led to death. This study also pointed to mild hematological adverse events.^[35] In some trials, death of patients after rituximab therapy was noted; however, some of them were due to background disorders like the study by H. L. Pellkofer *et al.*, in which several severe side effects in six of ten patients with NMO were seen. The death of one patient was related to past cardiovascular disorder. In another similar study, one death was reported 1 month after the first rituximab infusion due to cardiac and respiratory failure and no serious infections were noted. In a Chinese trial led by Vincent H. L. Ip *et al.*, infusions were tolerated well except in two patients who developed transient hypotension. In fact, no patient developed opportunistic infection during the follow-up period. The documentation of relapses within weeks of a rituximab infusion should prompt consideration of using methylprednisolone at the time of infusion.

CONCLUSION

Rituximab targets the CD20 antigen on B-cells and leads to profound B-cell depletion, principally over an antibody-dependent cell cytotoxicity mechanism and decreases attack frequency and severity in patients with NMO; however, it does not remove attacks, even when modifying treatment to achieve B-cell depletion. Most of the

investigations revealed that EDSS significantly in all patients with rituximab treatment will be decreased after treatment with rituximab. No new or enlarged lesions or pathological gadolinium enhancement was observed in serial brain and spinal cord MRIs, except for those observed concomitantly with clinical relapses and the median length of spinal cord lesions was significantly reduced after therapy.

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Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTION

- ME and OM contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- MS, MS,RN, MA and EF contributed in the design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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