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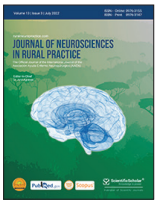

Original Article

Therapeutic response to rituximab in seropositive neuromyelitis optica: Experience from a tertiary care center in South India

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ABSTRACT

Objectives: Neuromyelitis optica (NMO) is a severe central nervous system demyelinating disease caused by autoantibodies to anti-aquaporin-4 immunoglobulin-G (AQP4-IgG). Rituximab, a monoclonal antibody targeting CD20 cells, is effective in neuromyelitis optica spectrum disorder (NMOSD) in several observational studies and small randomized controlled trials. However, this includes both AQP4-IgG antibody positive and negative cases. Whether rituximab is more effective in seropositive NMO is unknown. The aim of the study was to determine the efficacy of rituximab in seropositive NMO.

Materials and Methods: This single-center ambispective study with retrospective data collection and prospective follow-up included patients with NMOSD who were positive for AQP4-Ig-G and treated with rituximab. Efficacy outcomes assessed were annualized relapse rate (ARR), disability progression by expanded disability status scale (EDSS), very good outcome (defined as no relapse and an EDSS ≤3.5), and persistent antibody positivity. Safety was also monitored.

Results: Between June 2017 and December 2019, 15 AQP4-IgG-positive cases were identified. The mean (± SD) age was 36 ± 17.9 years and 73.3% were females. Transverse myelitis followed by optic neuritis was the most common presentations. Rituximab was initiated after a median period of 19-weeks from the disease onset. The mean number of rituximab doses received was 6.4 ± 2.3. After a mean follow-up duration of 107 ± 74.7 weeks from the first dose of rituximab, ARR significantly reduced from 0.5 ± 0.9 to 0.02 ± 0.08, difference 0.48 ± 0.86 (95% confidence intervals [CI], 0.0009–0.96; $P = 0.05$). The number of relapses also reduced significantly from 0.6 ± 0.8–0.07 ± 0.26, a difference of 0.53 ± 0.91 (95% CI, 0.026–1.05; $P = 0.041$). EDSS also significantly reduced from 5.6 ± 2.5–3.3 ± 2.9, a difference of 2.23 ± 2.36 (95% CI, 0.93–3.54; $P = 0.003$). Very good outcome was obtained in 73.3% (11 of 15); $P = 0.002$. AQP4-IgG remained positive in 66.7% (4 of 6) when repeated after a mean period of 149.5 ± 51.1 weeks after the first dose of rituximab. Neither pre-treatment ARR, EDSS, time to initiate rituximab, the total number of rituximab doses, or time to repeat AQP4-IgG were significantly associated with persistent antibody positivity. No serious adverse events were observed.

Conclusion: Rituximab exhibited high efficacy and good safety in seropositive NMO. Larger trials in this subgroup are warranted to confirm these findings.

Keywords: Demyelinating disease, Aquaporin 4, Immunotherapy, Transverse myelitis, Optic neuritis

INTRODUCTION

Neuromyelitis optica (NMO) is a demyelinating disease of the central nervous system (CNS) characterized by recurrent optic neuritis and transverse myelitis. In the international panel for NMO diagnosis (IPND) criteria by Wingerchuk *et al.*, other core features include area postrema involvement which presents as intractable hiccups and vomiting; acute brainstem syndromes; diencephalic syndrome, which presents as narcolepsy or endocrine dysfunction; and cerebral syndromes such as hemiparesis or other focal signs due to corticospinal or other white matter tract involvement.[1] First described by Devic in 1894, NMO is distinguished from other demyelinating disorders of the CNS by the presence of serum and cerebrospinal fluid (CSF) immunoglobulin-G (IgG) type antibodies against aquaporin-4 (AQP4) water channels.[2] AQP4-IgG is found in 88% of cases of NMO and has a specificity of 100%. Seronegative patients with typical clinico-radiological profile have been included in a broader category of NMO spectrum disorders (NMOSD).

AQP4-IgG is not just a diagnostic marker of NMO but has a direct pathogenic role. These antibodies target AQP4 in the astrocyte foot processes leading to complement-mediated-

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cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), oligodendrocyte death, demyelination, and neuronal death.[3] Passive transfer of AQP4-IgG in rodents causes lesions similar to NMO. Patients with high titers of AQP4-IgG develop severe optic neuritis, more extensive transverse myelitis, and larger cerebral lesions.[4] AQP4-IgG titers also correlate with disease relapses and a rapid reduction in the antibody by plasmapheresis reduces disease activity.

Histopathology from NMO lesions shows inflammatory infiltrate composed of granulocytes and macrophages with little CD3+ and CD8+ T cells and prominent perivascular immunoglobulin and complement deposition, suggesting a primary role for humoral immunity in the pathogenesis of NMO.[5] Rituximab is a humanized chimeric monoclonal antibody directed against CD20, a cell surface antigen found on pre and mature B-cells. Rituximab causes depletion of CD20+ B-cells by CDC, ADCC, and apoptosis, suppressing humoral immunity and is a promising treatment for NMO.[6] In a meta-analysis of 528 patients with relapsing NMOSD, which included both seropositive and seronegative patients, 62.9% achieved a relapse-free state[7] However, there are limited studies assessing the efficacy of rituximab in pure seropositive NMO. This study aims to assess the response to rituximab in AQP4-IgG positive NMO in terms of reduction in relapse rate, disability progression, and persistent AQP4-IgG positivity.

MATERIALS AND METHODS

Trial design

This was a single-center ambispective study with retrospective data collection and prospective follow-up to assess the efficacy of rituximab in seropositive NMO. The rationale for the study was that rituximab depletes B-cells, thereby reducing AQP4-IgG, the pathogenic antibodies in NMO. The trial was approved by the institutional ethics committee and was conducted in adherence with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines. Written informed consent was obtained from all the patients.

Participants

Both pediatric and adult patients were included if they had a clinicoradiological phenotype that met the IPND 2015 diagnostic criteria for NMO and was positive for AQP4-IgG, done with an indirect immunofluorescence assay, had received rituximab and had a follow-up of at least 4-months after the first dose of rituximab.[1] Exclusion criteria were patients who could not complete at least the induction regimen with 4-doses of rituximab, who did not have a documented baseline disability score and those with inadequate follow-up.

Intervention

Pre-treatment evaluation included a complete hemogram, electrolytes, liver and renal function tests, hepatitis B and C serologies, human immunodeficiency virus, chest X-ray, and an electrocardiogram. Premedication with intravenous 1 g paracetamol, 100 mg hydrocortisone and 45.5 mg of pheniramine maleate was given 30-min before the infusion. Rituximab induction was done at a dose of 375 mg/m^2 (maximum of 500 mg) once every week for 4-weeks.[8] The maintenance dose included the same single dose every 6-months. The infusion was started at a rate of 50 mg/h under continuous cardiac monitoring and titrated up by 50 mg/h every hour up to a maximum of 100 mg/h. Other immunosuppressants, if any, were allowed to be continued and their doses were titrated according to the clinical status. Follow-up was done monthly after the induction of rituximab for 3 months and every 2–3 months thereafter.

Assessments

Relapses, disability progression, very good outcome, and persistent antibody positivity were the four efficacy outcomes measured. Clinical relapse was defined as a new neurological deficit lasting at least 24 h with corresponding magnetic resonance imaging (MRI) abnormality, or if negative, an abnormal visual evoked potential (for optic neuritis). Relapses were measured as annualized relapse rate (ARR), defined as the number of relapses during a specified period adjusted to one year, calculated before and after initiation of rituximab, and as the total number of relapses. Disability was calculated using Kurtzke's expanded disability status scale (EDSS) and was measured before the initiation of rituximab and at the last follow-up.[9] Very good outcome was defined as no relapse and an EDSS of ≤3.5 (indicating fully ambulatory without aid and the disability does not interfere with activities of daily living). Repeat AQP4-IgG was done in some patients after initiating rituximab and the factors predicting persistent positivity were also analyzed.

Statistical analysis

Categorical variables were described as numbers with percentages, and numerical variables as mean with standard deviation or median with range. The efficacy outcomes, ARR, EDSS, and the number of relapses pre-and post-treatment with rituximab were described as differences with 95% confidence intervals (CI) and their significances were analyzed using paired *t*-tests. Very good outcome pre-and post-treatment was analyzed using McNemar's test. For persistence antibody positivity, the tests used were binary logistic regression for numerical independent variables, and Chi-square or Fischer's exact test for categorical variables. A two-sided $P < 0.05$ was considered statistically

significant. All analyses were performed using SPSS software (v.28.0.0.1, IBM).

RESULTS

Patients

Between June 2017 and December 2019, 27 AQP4-IgG-positive NMO patients were identified. Among them, 18 were treated with rituximab. Three patients had inadequate follow-up data and were excluded from the study. The baseline characteristics and clinical features of the rest 15 patients are given in [Tables 1 and 2]. The mean (±SD) age of the participants was 36 ± 17.9 years (range 11–62 years) and 73.3% (11 of 15) were females. The median time to diagnosis was 8-weeks (range 1–624 weeks). Transverse myelitis in 73.3% (11 of 15), followed by optic neuritis in 26.6% (4 of 15), were the most common presentations. A coexisting autoimmune disorder was found in 26.6% (4 of 15). This included 1 patient with SLE with positive antinuclear and anti-dsDNA antibodies, one with weakly positive anti-dsDNA and anti-SSA antibodies who did not have any symptoms of a systemic connective tissue disorder, and 2 patients with hypothyroidism. The mean number of relapses before initiating rituximab was 1.6 ± 0.8 and the ARR was 0.5 ± 0.9. The baseline EDSS was 5.6 ± 2.5, indicating moderate disability. Very good baseline status (no relapse and EDSS ≤3.5) was seen in 6.7% (1 of 15). Azathioprine in 20% (3 of 15) and mitoxantrone in 6.7% (1 of 15) were the immunosuppressants used before the initiation of rituximab. Concomitant prednisolone was used in 40% (6 of 15) at a mean dose of 7.5 ± 11.3 mg/day.

Efficacy

Rituximab was initiated after a median period of 19-weeks (range 2.7–625.3) from the disease onset, and after a median period of 7.1-weeks (range 0.4–26) from the last attack or relapse. The mean number of rituximab doses received was 6.4 ± 2.3. The mean follow-up duration was 107 ± 74.7 weeks from the first dose of rituximab [Table 3]. There was a significant reduction in ARR from 0.5 ± 0.9 to 0.02 ± 0.08, a difference of 0.48 ± 0.86 (95% CI, 0.0009 to 0.96; $P = 0.05$) [Table 4]. There was also a significant reduction in the number of relapses from 0.6 ± 0.8 to 0.07 ± 0.26, a difference of 0.53 ± 0.91 (95% CI, 0.026–1.05; $P = 0.041$). EDSS was also significantly reduced from 5.6 ± 2.5 to 3.3 ± 2.9, a difference of 2.23 ± 2.36 (95% CI, 0.93–3.54; $P = 0.003$). Very good outcome was obtained in 73.3% (11 of 15); $P = 0.002$. AQP4-IgG remained positive in 66.7% (4 of 6) when repeated after a mean period of 149.5 ± 51.1 weeks after the first dose of rituximab. Neither pre-treatment ARR, EDSS, time to initiate rituximab, the total number of rituximab doses, or time to repeat AQP4-IgG were significantly associated with persistent antibody positivity.

Safety

Rituximab was generally well tolerated in most patients. Infusion reactions in 26.6% (4 of 15) were the most common,

Table 1: Baseline characteristics of the patients.

Characteristic	
Age - yr	36±17.9
Female sex–no (%)	11 (73.3)
EDSS	5.6±2.5
ARR	0.5±0.9
No of relapses before Rtx	0.6±0.8
Very good baseline (no relapse and EDSS≤3.5) no (%)	1 (6.7)
Previous immunosuppressants–no (%)	
Azathioprine	3 (33.3)
Mitoxantrone	1 (6.7)

*Values are mean±SD unless specified otherwise. no: Number, Rtx: Rituximab, yr: Year, EDSS: Expanded disability status scale, ARR: Annualized relapse rate

Table 2: Clinical and paraclinical features of the patients.

Characteristic	
Time to diagnosis–median (range) - weeks	8 (1–624)
Demyelinating phenotype at onset–no (%)	
Optic neuritis	4 (26.6)
Transverse myelitis	11 (73.3)
Area postrema	1 (6.6)
Brainstem	3 (20)
Diencephalon	0
Cerebral	0
Symptoms and signs at onset–no (%)	
Visual	4 (26.6)
Motor	11 (73.3)
Cerebellar	1 (6.6)
Sensory	12 (80)
Cranial nerve	2 (13.2)
Urogenital	5 (33.3)
Pyramidal signs	4 (26.6)
Tonic spasms	3 (20)
Pruritus	1 (6.6)
Hiccups/Vomiting	1 (6.6)
ESR - mm/1st h (n=12)	38.3±27.9
Coexisting autoimmune disorder–no (%)	4 (26.6)
CSF (n=8)	
Total cells–cells/mm^3	2±6
Protein–mg/dL	45.5±33.7
OCB–no/total no (%)	0/3 (0)
MRI changes–no (%)	
Optic nerve	4 (26.6)
Subcortex	2 (13.2)
Periventricular	1 (6.6)
Brainstem	3 (20)
Spinal cord	11 (73.3)

no: Number, CSF: Cerebrospinal fluid, ESR: Erythrocyte sedimentation rate, MRI: Magnetic resonance imaging, OCB: Oligoclonal bands

which included transient hypotension, tachycardia or chills, which subsided with temporary discontinuation of the infusion and reinitiation at a lower rate. These were observed only during the first infusion and subsequent infusions were uneventful. Upper respiratory infection occurred in 13.3% (2 of 15) within 2-weeks of the infusion. Serious adverse events leading to discontinuation of rituximab did not occur in any patient. There was one death (due to a road traffic accident) which was unrelated to the illness.

DISCUSSION

In this study of patients with AQP4-IgG positive NMO, rituximab resulted in a significant reduction in ARR, number of relapses, improvement in EDSS, and achieved a very good outcome in 73.3% (11 of 15). A cutoff EDSS of ≤3.5 was used to define the very good outcome, as this represents the upper limit of a functional stage where ambulation is independent and unrestricted, despite mild to moderate disability on examination, thus being able to carry out activities of daily living. A relapse occurred only in 1 of 15 patients during a mean follow-up of nearly 2-years, indicating a relapse-free rate of 93.3% (14 of 15). This occurred in a 25-year-old female whose initial presentation was a longitudinally extensive transverse myelitis (LETM), was treated with methylprednisolone followed by 6 doses of rituximab (4 inductions and 2 maintenance). After 1-month of the sixth dose of rituximab and while on 5-mg prednisolone, she presented with acute bilateral sensorineural hearing loss. She improved with methylprednisolone and the maintenance dose of prednisolone was increased. She continued to receive three more scheduled rituximab doses till the last follow-up and had no more relapses.

Table 3: Treatment parameters.

Parameter	
Time to initiate rtx from disease onset –weeks–median (range)	19 (2.7–625.3)
Time to initiate rtx from last attack/ relapse–weeks–median (range)	7.1 (0.4–26)
Total no of rtx doses	6.4±2.3
Follow-up from disease onset–weeks	196.8±175.5
Follow-up after first rtx-weeks	107±74.7
EDSS at last follow-up	3.3±2.9
ARR on rtx	0.02±0.08
Total relapses on rtx–mean (range)	0.07 (0–1)
Very good outcome–no (%)	11 (73.3)
Repeat antibody positive - no/total no (%)	4/6 (66.7)
Maintenance prednisolone**–no (%)	6/15 (40)
Prednisolone dose - mg	7.5±11.3

*Values are mean±SD unless specified otherwise, **One patient with SLE-NMO was also on hydroxychloroquine with prednisolone, no number, Rtx: Rituximab; yr: Year, EDSS: Expanded disability status scale, ARR: Annualized relapse rate

Even though there are only a few randomized control trials of rituximab in NMO, several observational studies and meta-analyses suggest its good efficacy.[7,8,10-12] In the most recent meta-analysis of 577 patients with NMOSD, which included about 75% seropositive cases, rituximab led to a mean reduction of ARR and EDSS of 1.56 and 1.16, respectively.[7] Even though the mean decrease in ARR in our study was 0.48, which is numerically less than that in the meta-analysis, the mean baseline ARR in our population was only 0.5; hence, a 0.48 reduction translates to a 96% reduction of ARR. Our study's mean reduction in EDSS was 2.23, which was higher than that in the meta-analysis. These indicate that rituximab is more effective in seropositive NMO than seronegative NMOSD. As opposed to seropositive NMO, seronegative NMO has been found to have a male-to-female ratio of 1:1, more opticospinal presentations and less severe visual impairment.[13,14] It is postulated that seronegative NMO is a T-cell mediated disease, where T helper (TH) 17 cells secrete interleukin-17, disrupt the blood-brain barrier and trigger CNS inflammation through granulocyte recruitment.[15] This was further supported by the fact that lymphocytapheresis exhibited high efficacy in some cases of seronegative NMO unresponsive to methylprednisolone, plasma exchange and immunoglobulin.[16]

There are three dosing strategies for rituximab; one where rituximab is given in a fixed schedule every 6-months, another by monitoring CD19 cells and timing the infusion once the cell count is above 1% of peripheral blood mononuclear cells (PBMC), and the other by monitoring CD27 cells and infusing when CD27 cell count is above 5% of PBMC.[17] The fixed dosing schedule is based on the

Table 4: Efficacy outcomes.

Characteristic	Pre-treatment	Post-treatment	Difference	*P*-value
ARR	0.5±0.9	0.02±0.08	0.48±0.86 (0.0009–0.96)	0.05
Number of relapses	0.6±0.83	0.07±0.26	0.53±0.91 (0.026–1.05)	0.041
EDSS	5.6±2.5	3.3±2.9	2.23±2.36 (0.93–3.54)	0.003
Very good outcome–no (%)	1 (6.7)	11 (73.3)	10 (66.7)	0.002

*Values are mean±SD with 95% confidence intervals in brackets unless specified otherwise, ARR: Annualized relapse rate, EDSS: Expanded disability status scale

observation that, on average, rituximab leads to B-cell depletion for 3–6-months. In one study, it was seen that the 6-month infusion was enough in most patients, but about 17% repopulate B-cells before this period and are at risk of relapse.[18] In another study where timing the infusion based on CD27 cell monitoring was compared to a fixed schedule every 6-months, a relapse-free condition was equal between the two groups with fewer total rituximab infusions in the monitored group.[19] Our study also supports the fixed schedule regimen, achieving a relapse-free rate of 93.3%. A relapse while on this fixed-dose regimen should not be taken as a rituximab failure but as an indication to shift the strategy to one of the B-cell monitoring regimes.

In our study, a repeat AQ4-IgG, done after a mean period of nearly 3-years after the first dose of rituximab, was negative in 33.3% (2 of 6) patients tested. None of the parameters including ARR, EDSS, total rituximab doses or additional prednisolone, were significantly associated with persistence antibody positivity. In one study, even though a prompt and rapid decline in AQP4 antibody at a median of 8%/week was seen with immunosuppressive therapy, the antibodies did not completely disappear in most patients while on rituximab, despite low CD19 cells.[20] This is because although rituximab completely depletes CD20-positive peripheral B-cells, plasma cells that ultimately secrete the antibodies are unaffected. Moreover, a class of long-lived plasma cells persists throughout the host's lifespan, which continues to secrete antibodies. In our study, the first patient whose repeat antibody was negative after 20-months had received 7 doses of rituximab with a maintenance dose of 7.5 mg of prednisolone and was in remission. The second patient whose repeat antibody was negative was a 24-year-old female whose first attack was an LETM and rituximab was initiated within 4-weeks of disease onset. After a total of 9 doses of rituximab, and while on 5-mg prednisolone, she had a relapse characterized by acute bilateral sensorineural deafness. A repeat antibody was done at this time and was negative. This was unusual as AQP4-IgG antibodies being pathogenic, antibody titers correlate with disease activity and an increase in antibody titers up to 3-times are seen heralding a relapse in one study.[20] However, it is noted that a relapse followed not all cases of rising antibody titers.[12] In our study, the antibody was measured only in the serum and not in the CSF. A rise in titers of AQP4-IgG before a relapse has been noted only in CSF and not in the sera in some studies.[21,22] Another explanation for this paradoxical negativity of antibody during the relapse in our study might be related to the semi-quantitative method used to detect the antibody where a mere absence might not indicate the actual level of antibody. The first attack of LETM in this patient might have been a more aggressive one with high titers of antibody. In contrast, the second relapse, which was clinically less severe, might have had lower titers of antibody and hence undetectable by our method. Furthermore, it is often seen that antibody levels were higher during remission in some patients than in a relapse, low titers were associated with clinical relapse and antibody levels fluctuated during rituximab therapy without a clear correlation with a relapse.[11,20] These indicate that apart from AQP4 antibodies, clinical relapse involves an interplay of other factors such as disease-specific T-cells, exogenous triggers, and alterations in the blood-brain barrier. The only common factor among these two patients with repeat antibody negativity was that they were also on maintenance prednisolone. In our study, even though a numerically lesser number of patients with persistent antibody positivity were on prednisolone (25% vs. 100%), it did not reach statistical significance. This is consistent with the observation that antibody levels decline more with combined immunosuppression and withdrawal of one of the agents is associated with a rise in antibody titer and clinical relapse.[20]

Despite its proven efficacy, the FDA has not approved rituximab for the treatment of NMO. Eculizumab, a terminal complement inhibitor, was shown to be highly efficacious in NMOSD with a relapse-free rate of 96.9% and was the first FDA-approved therapy for NMOSD.[23] Subsequently, inebilizumab, a monoclonal antibody binding to CD19 and depleting a wider range of lymphocytes than rituximab, and satralizumab, an interleukin-6 inhibitor, were shown to be effective in NMOSD and were approved by the FDA.[24-26] However, the exorbitant cost of these novel therapies and their unavailability in India makes these unviable options. In this context, rituximab is a promising drug for NMO in our country.

There are several limitations to this study. First, this was a non-randomized trial and hence no direct conclusions regarding the efficacy can be made. Rituximab was given in only 66.6% (18 of 27) seropositive NMO patients identified during the study period, since there were no strict criteria set regarding the choice of immunotherapy after an attack of NMO. The sample size was small and a repeat AQP4-IgG was done only in some cases, limiting the power of the study. Finally, there were no MRI endpoints, which could have assessed how the lesions evolved in response to rituximab. Nevertheless, the high retention rate of the subjects and relatively adequate follow-up is the strengths of the study.

CONCLUSION

Rituximab was highly efficacious in reducing relapses and preventing disability progression, and is well tolerated in seropositive NMO, but did not result in significant AQ4-IgG negativity. A fixed-dose schedule of 6-monthly infusion without monitoring CD19 or CD27 cells achieved a good relapse-free rate. Larger trials with longer duration of follow-up are necessary to confirm these findings. Further studies

on rituximab as a monotherapy without prednisolone are also warranted in this subgroup.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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