Treatment of Neuromyelitis Optica With Rituximab

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Retrospective Analysis of 25 Patients

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Background: Neuromyelitis optica (NMO) is an uncommon, life-threatening inflammatory demyelinating disorder. Recently, much has become known about its immunopathogenesis. However, optimal treatments, with expected outcomes, have not been established.

Objective: To evaluate the use and efficacy of rituximab for treating NMO.

Design: Retrospective multicenter case series of NMO patients treated with rituximab.

Setting: Seven tertiary medical centers in the United States and England.

Patients: Twenty-five patients (including 2 children), 23 of whom experienced relapses despite use of other drugs before rituximab. Extended follow-up of 7 previously reported patients is included.

Interventions: Infusions of rituximab at median intervals of 8 months.

Main Outcome Measures: Annualized relapse rate and disability (expressed as Expanded Disability Status Scale score).

Results: At a median follow-up of 19 months, the median annualized posttreatment relapse rate was lower than the pretreatment rate (0 [range 0-3.2] vs 1.7 [range, 0.5-5] relapses, $P<.001$). Disability improved or stabilized in 20 of 25 patients (80%, $P=.02$). Two patients died during the follow-up period, 1 owing to a brainstem relapse and 1 owing to suspected septicemia. Infections were reported in 20% of patients.

Conclusions: In NMO, treatment with rituximab appears to reduce the frequency of attacks, with subsequent stabilization or improvement in disability.

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NEUROMYELITIS OPTICA (NMO) is an inflammatory demyelinating disorder, usually relapsing, that targets the optic nerves and spinal cord, resulting in attack-related accrual of disability. It is probably the same disorder as Asian opticospinal multiple sclerosis in those whose spinal cord lesions extend 3 or more segments during acute attacks. Compared with typical multiple sclerosis, NMO is more rapidly disabling; 50% of patients must use a wheelchair and 62% become functionally blind (visual acuity of 20/200 or worse) at 5 years.[1] Treatment of NMO with interferon beta appears to be substantially less effective than immunosuppressive therapy[2] and possibly even deleterious,[3] which further underscores the difference between NMO and typical multiple sclerosis. Randomized controlled trials have not been conducted on NMO, and treatment options are based on small case series that used immunosuppressant medications, including azathioprine,[4] mitoxantrone,[5] and mycophenolate mofetil.[6] Despite use of these drugs, patients with NMO often experience ongoing disease activity. Open label use of rituximab (Rituxan; Biogen Idec, Cambridge Massachusetts/Genentech, San Francisco, California), a monoclonal antibody against $CD20^+$ B cells, was reported to be potentially beneficial in patients who are refractory to a variety of immunotherapies.[7,8] Given the lack of proven efficacious treatments, this case series led us to use rituximab in patients with NMO, even as a first-line

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treatment. We describe our multicenter, longitudinal experience of the effectiveness and adverse effects of rituximab in 25 cases of NMO.

METHODS

This is a retrospective case series of the use of rituximab in NMO. Investigators from 20 centers who attended an exploratory meeting about a potential clinical trial of a new humanized monoclonal antibody that, like rituximab, recognizes the CD20 protein were approached to participate in this study. Seven centers responded to the request. Investigators recalled and contributed information on all the patients to whom rituximab was administered for NMO (University of California–San Francisco, San Francisco [n=7]; Stony Brook Hospital, Stony Brook, New York [n=6]; Mayo Clinic, Rochester, Minnesota [n=5]; Mayo Clinic, Scottsdale, Arizona [n=2]; The Walton Center, Liverpool, England [n=2]; Mellen Center, Cleveland Clinic, Cleveland, Ohio [n=2]; and Mount Sinai Hospital, New York, New York [n=1]). University of California–San Francisco provided extended follow-up on 7 previously reported patients.[7] New patients from University of California–San Francisco were not included because of contemporaneous recruitment of patients with NMO into a clinical trial. Local institutional review board approval was obtained at each center and informed consent was obtained from patients or their next of kin. All patients with relapsing NMO or longitudinally extensive transverse myelitis[9] who were treated with at least 1 dose of rituximab and who had at least 6 months of follow-up were included. Patients who did not meet these criteria were excluded. Given the small number of patients treated at each center, we are reasonably confident, but not absolutely certain, that other eligible patients were not excluded. Completed case report forms were analyzed at the Mayo Clinic in Rochester. All patients who were reported to the analysis team by the treating hospitals were found to be eligible and were included. Statistical analysis was performed using JMP, version 6.0 (SAS, Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS

All 25 patients qualified for inclusion in the study, according to the inclusion and exclusion criteria. There were 3 men, 20 women, and 2 girls. The median age of the patients was 38 years (range, 7-65 years). Two children received their initial rituximab treatment at age 7 years (patient 8) and 14 years (patient 11). Twenty-three patients had NMO and 2 had NMO-IgG–seropositive recurrent longitudinally extensive transverse myelitis. The median interval from onset of NMO to treatment with rituximab was 4.5 years (range, 0.8-17 years). The clinical and demographic profiles of the patients are outlined in the **Table**. Seventy percent of patients assessed were positive for NMO-IgG (14 of 20 patients). Seven of 8 patients from the previously reported case series were included.[7] One patient from the initial study was lost to follow-up despite multiple attempts to contact her. Rituximab was used in 23 patients owing to failure of other medications. In 19 patients, more than 1 treatment was used before treatment with rituximab. Rituximab was used as a first-line therapy in 2 patients.

TREATMENT WITH RITUXIMAB

Two rituximab regimens were used: (1) 375 mg/m^2 infused once per week for 4 weeks (n=18)[10] and (2) 1000 mg infused twice, with a 2-week interval between the infusions (n=4).[11] These regimens were based on rituximab's use in rheumatology,[11] hematology,[10] and the previously reported series of patients with NMO.[7] Local practice determined selection of the regimen. The specific treatment regimen for the remaining 3 patients was not available.

Seventeen patients were retreated with rituximab: 8 had 4 additional doses of 375 mg/m^2 and 7 had 2 1000- mg doses 2 weeks apart. Data regarding the subsequent dosing regimen were unavailable for 2 patients. Other immunotherapies with rituximab were used in 5 patients: azathioprine with prednisone (n=1), prednisone (n=3), and interferon beta (n=1).

The median interval between the last relapse and start of treatment was 1 month (range, 0-7 months; mean, 1.5 months). Twenty of the 25 patients received treatment within 2 months of their last relapse. The median interval between rituximab treatments was 8 months (range, 4-26 months). Subsequent treatments were either planned at 6- to 12-month intervals or were administered after relapse or when CD19$^+$ B cells became detectable. Counts of CD19 cell markers were not routinely monitored in all patients, and a threshold value was not used to determine the timing of retreatment.

FOLLOW-UP

The median follow-up interval after initial rituximab treatment was 19 months (range, 6-40 months). Eighteen patients planned to continue treatment with rituximab at their last follow-up and 15 received rituximab during the preceding 6 months of follow-up.

Seven patients discontinued treatment. The reasons for discontinuation were death (n=2 [patients 5 and 10]), relapses (n=2 [patients 18 and 22]), pregnancy (n=1 [patient 14]), and other (n=2 [patients 13 and 20]).

After experiencing relapses after treatment with rituximab, 2 patients started other treatments (patients 18 and 22). Patient 18 required plasmapheresis every 6 weeks in conjunction with pulsed intravenous corticosteroids twice per month and mycophenolate mofetil to maintain remission from additional relapses. Patient 22 started treatment with cyclophosphamide after her third relapse.

Patient 20, who took azathioprine throughout the study, was averse to parenteral administration of drugs and wished to restart treatment with azathioprine. After 2 minor relapses, the dose of azathioprine was increased; the patient was relapse-free when this manuscript was written. One patient had a planned pregnancy (patient 14) and discontinued treatment. Patient 13 discontinued treatment with rituximab and did not receive other immunosuppressive treatment despite having a minor relapse (**Figure**). However, after completion of this analysis, she was readmitted with a severe spinal cord relapse 2 years after her last infusion of rituximab (not shown in the Figure) and has now resumed taking rituximab; this relapse was not included in the analysis of the relapse rate.

Table. Clinical Profile of Patients Treated With Rituximab

Patient No./Sex/Age at First Rituximab Treatment, y	Diagnosis	Disease Duration at First Rituximab Treatment, mo	NMO-IgG Status	LETM on MRI	Drugs Used Before Rituximab (Duration of Treatment, mo)	Concomitant Immunotherapy
1/F/49	NMO	4.84	–	+	Glatiramer acetate (7)	
2/M/28	NMO	5.25	+	+	Interferon beta (24) Azathioprine (28) Intravenous immunoglobulins (23)	
3/F/19	NMO	4.62	+	+	Azathioprine (9) Interferon beta (7)	
4/F/43	NMO	2.09	–	+	None	
5/F/43	NMO	17.22	Test not done	+	Azathioprine (U) Prednisone (U) Mitoxantrone (2) Cyclophosphamide (U) Mycophenolate mofetil (U)	
6/M/22	NMO	15.79	+	+	Azathioprine(U) Prednisone (U) Methotrexate (U)	
7/F/40	NMO	6.77	Test not done	+	Glatiramer acetate (9) Azathioprine (13) Interferon beta (3) Mitoxantrone (2) Azathioprine (20) Prednisone (20)	Azathioprine
8/F/7	NMO	4.17	+	–	Prednisone (3)	
9/F/21	NMO	7.92	+	+	Interferon beta (6) Azathioprine (27) Cyclophosphamide (1) Mitoxantrone (2)	
10/F/53	NMO	3.68	+	+	Mitoxantrone (5) Azathioprine (6)	
11/F/14	NMO	7.25	–	U	Prednisone (7) Intravenous immunoglobulins (U)	Prednisone, azathioprine
12/F/50	NMO	0.83	Test not done	+	U	
13/F/33	NMO	2.89	+	+	Interferon beta (U) Intravenous immunoglobulins (U)	
14/F/28	NMO	6.08	Test not done	+	Interferon beta (60) Azathioprine (72) Prednisone (24) Intravenous immunoglobulins (15)	
15/F/18	NMO	8.17	+	+	Interferon beta (102) Mitoxantrone (3) Intravenous immunoglobulins (4)	Interferon beta
16/F/19	NMO	6.32	+	+	Interferon beta (12) Glatiramer acetate (3) Interferon beta (45) Intravenous immunoglobulins (7) Mitoxantrone (3)	
17/F/22	NMO	7	+	+	Interferon beta (12) Azathioprine (14) Mitoxantrone (22) Azathioprine (4)	
18/F/52	NMO	4.25	–	+	Interferon beta (26)	
19/F/54	NMO	1.17	+	+	Azathioprine (5) Prednisone (5)	Prednisone
20/F/43	Relapsing myelitis	4.13	+	+	Hydroxychloroquine (1) Azathioprine (53) Prednisone (12)	Prednisone
21/F/43	Relapsing myelitis	2.62	+	+	Cyclophosphamide (22)	
22/F/35	NMO	3.63	–	+	Glatiramer acetate (24)	
23/F/47	NMO	3.1	+	+	Prednisone (3) Azathioprine (6)	
24/M/62	NMO	2.88	Test not done	+	Interferon beta (4) Azathioprine (2)	
25/F/24	NMO	4.93	–	+	Azathioprine (12) Prednisone (12) Interferon beta (33) Intravenous immunoglobulins (1)	

Abbreviations: LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; U, unknown; +, positive; –, negative.

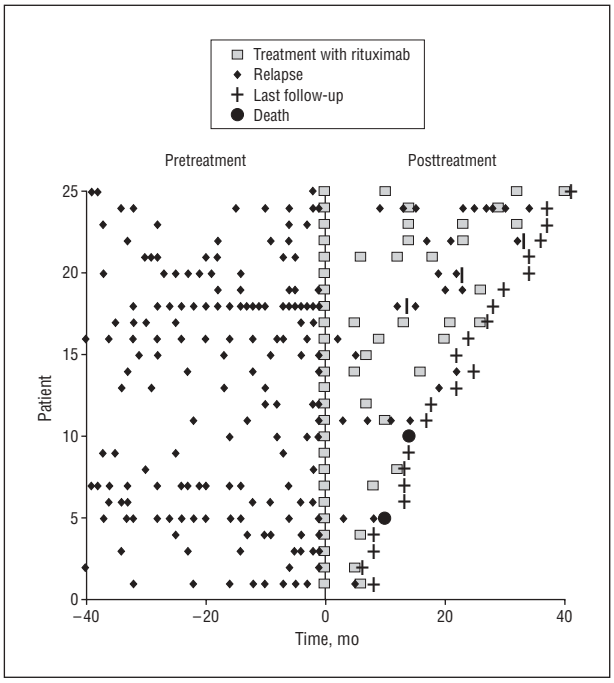

Figure. Relapses in patients with neuromyelitis optica before and after treatment with rituximab.

TREATMENT EFFICACY

Relapse Rates

Relapses before and after treatment are represented in the Figure. All relapses after onset of rituximab treatment were considered. However, if new treatments were started, only relapses until the start date of the new treatment were included (patients 18, 20, and 22). Relapses in patients who stopped taking rituximab but who were not undergoing any other treatments were included. For all 25 patients, the median annualized pretreatment relapse rate was 1.7 relapses (range, 0.5-5 relapses) and the median annualized posttreatment rate was 0 relapses (range, 0-3.2 relapses, $P<.001$, Wilcoxon signed-rank test) at a median follow-up of 19 months. The following sensitivity analyses were performed to address whether these results were biased by including patients who died, were followed up for less than 1 year after treatment with rituximab, or received concomitant treatment with other immunotherapies. If the 2 patients who died (patients 5 and 10) were excluded (n=23), the median pretreatment annualized relapse rate was 1.7 relapses (range, 0.6-4.9 relapses) and the posttreatment was 0 relapses (range, 0-3.2 relapses) ($P<.001$). If the 5 patients who were undergoing additional immunotherapies (patients 7, 11, 15, 19, and 20) and the 2 who died were excluded (n=18), the median pretreatment relapse rate was 1.7 (range, 0.7-4.9) and the median posttreatment relapse rate was 0 (range, 0-2.9) at a median follow-up of 18 months. If the patients who were followed up for less than 1 year were also excluded (patients 1, 2, 3, and 4) along with those taking additional immunotherapies (n=5) and those who died (n=2), the median pretreatment and posttreatment relapse rates were 1.5 (range, 0.7-4.9) and 0 (range, 0-2.9), respectively, at a median follow-up of 22 months in the remaining 14 patients.

Disability

Two patients died (patients 5 and 10). The median Expanded Disability Status Scale (EDSS) score at the start of treatment with rituximab (n=25) was 7 (range, 3-9.5) and at last follow-up at a median of 19 months was 5 (range, 3-10) ($P=.02$). The EDSS scores stabilized in 9 patients and improved in 11. In 5 patients (patients 3, 5, 10, 13, and 20), EDSS scores worsened.

ADVERSE EVENTS OBSERVED DURING TREATMENT AND FOLLOW-UP

Transient infusion-related adverse effects occurred in 7 of 25 patients (28%) and were not dose-limiting. New or reactivated infections developed in 5 of 25 patients (20%) and included herpes simplex (cold sore) and positive tuberculin skin test (n=1), herpes zoster (n=1), recurrent *Clostridium difficile* colitis (n=1), a cutaneous fungal infection (n=1), and fatal urinary tract–related septicemia (n=1). Worsening of preexisting seborrheic dermatitis occurred in 1 patient.

DEATHS

Patient 5 developed recurrent *C difficile* colitis after her first rituximab infusion followed by a urinary tract infection. She died 9 months after the last dose following a severe relapse; she had a brainstem lesion that extended into the hypothalamus and thalamus on magnetic resonance imaging. Clinical manifestations were lethargy, obtundation, electrolyte imbalance, and hypothermia. $CD19^+$ B cells were not detectable 2 months before her death (7 months after last infusion).

Patient 10 died 6 months after the last dose of rituximab. She was obtunded and suspected of being septic. An autopsy of the brain and spinal cord showed confluent demyelination from the lumbar spinal cord to the cervical cord with necrosis and cavitation, perivascular lymphoid infiltrate, and macrophage infiltrates. Both optic nerves were atrophic and had lymphocyte and macrophage infiltrates. The brain did not show any pathology. $CD19^+$ B cells were undetectable 5 months after her last infusion (1 month before death). Her total lymphocyte count was 900/μL (to convert to $\times 10^9$ per liter, multiply by 0.001) before death (normal, 900-2900/μL) compared with 2730/μL before starting rituximab. She also had low IgA, IgG, and IgM concentrations 1 month before her death. She was treated with mitoxantrone before initiation of rituximab.

COMMENT

Neuromyelitis optica is a relapsing disorder with rapid accrual of attack-related disability and a high, early mortality rate.[1] Controlled trials of treatments to prevent relapses are unavailable, and treatment is based on case series and expert opinion. Although 2 cases were reported to enter remission with the use of glatiramer acetate,[12,13] immunomodulatory medications (interferon beta or glatiramer acetate) do not appear to be beneficial in larger case series.[2,3] Immunosuppressive drugs are the mainstay of treatment of NMO. Azathioprine[4] is the most widely used medi-

cation. Cyclophosphamide, mitoxantrone,[5] cyclosporine, methotrexate, and mycophenolate mofetil[6] have also been used.[14] However, patients commonly relapse on these treatments; relapses with brainstem or cervical cord involvement are a frequent cause of death in NMO.[1]

In this retrospective, multicenter case series, we evaluated the use of rituximab in patients with NMO who were largely refractory to other treatments. Relapse rates improved and disability stabilized or improved in 20 of 25 patients (80%), a rate that is similar to previously reported observations.[7]

Although the infections cannot be definitively classified as opportunistic, the death of 1 patient owing to sepsis and the occurrence of infections in others raise important concerns about rituximab's safety in this specific disease setting. Patient 10 died following a presumed urinary tract infection and had reduced lymphocyte counts and immunoglobulin concentrations. It is possible that treatment with rituximab and/or prior treatment with mitoxantrone contributed to this patient's sepsis.

We did not attempt to identify predictive factors of a beneficial response to rituximab treatment. The small size of the study, retrospective acquisition of data, and positive treatment response in 80% of patients precludes such an analysis. We did not compare the 2 regimens owing to the differing number of patients in the 2 groups and the switching between the 2 regimens for subsequent treatments in some patients.

It is unclear whether rituximab should be the first treatment for NMO. Comparative studies of the immunosuppressive treatments used for NMO have not been undertaken. Most patients in this series are from a selected population with treatment-refractory NMO. It is possible that patients who have never undergone treatment may benefit from more widely available and less expensive immunosuppressive medications. Furthermore, even in this small group, there are apparent rituximab treatment failures, demonstrating that it is not effective in all patients. A recent case report of 2 patients with variable responses to rituximab highlights this point.[8]

Safety concerns regarding rituximab persist. The relative risk of infections with rituximab vs other immunosuppressive treatments of NMO is unknown. Recent reports of progressive multifocal leukoencephalopathy in 2 patients with systemic lupus erythematosus, 1 patient with systemic vasculitis, and 23 patients with lymphoma treated with rituximab are concerning.[15] However, these patients received treatment with other immunosuppressive medications, either sequentially or combined with rituximab. Lymphomas and systemic lupus erythematosus are thought to predispose individuals to progressive multifocal leukoencephalopathy, irrespective of treatment. Progressive multifocal leukoencephalopathy has also been associated with azathioprine,[16,17] cyclosporine,[18,19] cyclophosphamide,[20] and mycophenolate mofetil.[21]

Rituximab treatment is more expensive[22] than generic immunosuppressive drugs, such as azathioprine. However, the higher cost may offset the cost of hospitalizations for relapses and plasma exchanges if rituximab is more effective.

Our study is limited by the retrospective nature of the case series, which is based on the clinical experience with rituximab at 7 centers, and several important caveats should be mentioned. First, 2 treatment regimens were used, though the total dose administered to each patient was similar. Second, the intervals between courses of treatment varied. Third, it is possible that regression to the mean contributed to the decline in relapse rates. However, we believe that this is unlikely because there was no specific relapse requirement preceding rituximab treatment for inclusion in this case series and because the pretreatment relapse rates were determined from disease onset rather than from a fixed period immediately preceding rituximab therapy. Fourth, the interval between rituximab and previous drugs was often short, and it is possible that some of the effects that were attributed to rituximab could be due to residual benefits from other medications. Fifth, rituximab was used with other drugs in 5 patients. Sixth, $CD19^+$ B-lymphocyte counts were not measured to assess efficacy of treatment and timing of retreatment. Lastly, the pretreatment EDSS score may have been determined immediately postrelapse, while the last available EDSS score may have been determined during a period of stability, thus showing improvement attributable to recovery from an attack.

Despite these limitations, we feel that the data are credible, particularly considering the robust suppression of disease activity in patients with NMO following rituximab treatment. Recently, much has been learned about the pathogenesis of NMO.[23] However, data on treatment of NMO are sparse, and randomized, controlled trials on this disease have never been performed. This is the largest case series of a single drug treatment, particularly in the subgroup of patients with NMO who are refractory to conventional treatment in whom the risk of mortality is high. Controlled trials are difficult to organize owing to a variety of reasons, including the rarity of the disease, need for early treatment, and high morbidity from relapses. Given the absence of such controlled trials, studies such as this provide at least anecdotal evidence to help guide clinicians in selecting treatments for this potentially life-threatening disease.

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