Neuromyelitis optica (NMO) is an autoimmune inflammatory disease of the central nervous system characterized by severe attacks of optic neuritis and longitudinally extensive transverse myelitis. Recently, the demonstration of a pathogenic role for the anti-aquaporin 4 (AQP4) antibody in NMO has marked a major advance in the understanding of the disease. The critical role of B cells in the pathogenesis of NMO previously has been suggested by an association with the anti-AQP4 antibody.

Rituximab, a monoclonal antibody that selectively targets CD20+ B cells, has exhibited promising clinical efficacy for the prevention of relapses in patients with NMO. In 2005, Cree and colleagues reported the first open-label study evaluating rituximab therapy in patients with NMO; their study included 8 patients. In 2008, the beneficial effects of rituximab were reported in a retrospective multicenter study of 25 patients with NMO (median duration of treatment, 19 months). In 2011, favorable outcomes of repeated treatment with rituximab were reported in 2 studies of patients with NMO, including 23 and 10 patients.

To date, it has generally been accepted that repeated treatment with rituximab is necessary to prevent NMO relapse, but questions remain as to how and when patients with NMO should receive further treatment. Common practice includes the repeated administration of a single course (375 mg/m²/wk for 4 weeks or 1000 mg infused twice, with 2 weeks between treatments) of rituximab as maintenance therapy whenever the frequency of reemerging CD27+ memory B cells in peripheral blood mononuclear cells, as measured with flow cytometry, exceeded 0.05% in the first 2 years and 0.1% thereafter.

IMPORTANCE A previous 2-year analysis of repeated rituximab treatment in patients with neuromyelitis optica (NMO) revealed significant improvements in relapse rates and disability. We report the findings from the longest follow-up of rituximab treatment in NMO, which provide reassurance regarding the long-term efficacy and safety of rituximab in NMO.

OBJECTIVE To report the results of rituximab treatment in patients with relapsing NMO or NMO spectrum disorder (NMOSD) for a median of 60 months.

DESIGN, SETTING, AND PARTICIPANTS Retrospective case series in an institutional referral center for multiple sclerosis, including 30 patients with relapsing NMO or NMOSD.

INTERVENTIONS After induction therapy, a single infusion of rituximab (375 mg/m²) as maintenance therapy was administered whenever the frequency of reemerging CD27+ memory B cells in peripheral blood mononuclear cells, as measured with flow cytometry, exceeded 0.05% in the first 2 years and 0.1% thereafter.

MAIN OUTCOMES AND MEASURES Annualized relapse rate (ARR), disability (Expanded Disability Status Scale score), change in anti-aquaporin 4 antibody, and safety of rituximab treatment.

RESULTS Of 30 patients, 26 (87%) exhibited a marked reduction in ARR over 5 years (mean [SD] pretreatment vs posttreatment ARR, 2.4 [1.5] vs 0.3 [1.0]). Eighteen patients (60%) became relapse free after rituximab treatment. In 28 patients (93%), the disability was either improved or stabilized after rituximab treatment. No serious adverse events leading to discontinuation were observed during follow-up.

CONCLUSIONS AND RELEVANCE Repeated treatment with rituximab in patients with NMOSD over a 5-period, using an individualized dosing schedule according to the frequency of reemerging CD27+ memory B cells, leads to a sustained clinical response with no new adverse events.
between doses) every 6 to 12 months.\textsuperscript{3-7} We reported elsewhere\textsuperscript{8} a significant clinical effect of repeated rituximab treatment in 30 patients with NMO spectrum disorder (NMOSD). Patients received a single additional infusion of rituximab (375 mg/m\textsuperscript{2}) as maintenance therapy on the reappearance of peripheral CD27\textsuperscript{+} memory B cells.\textsuperscript{8} During a 2-year period, the relapse rate was reduced by 88%, and, overall, 70% of patients became relapse free.\textsuperscript{8} Our strategy could achieve effective disease control with a much lower cumulative dose than used in prior studies.\textsuperscript{3-6} Moreover, memory B-cell depletion in peripheral blood was shown to be associated with the clinical response to rituximab.\textsuperscript{8}

Although available clinical data regarding treatment with repeated cycles of rituximab show clinical efficacy and an acceptable safety profile, the long-term efficacy and safety of rituximab in patients with NMO has yet to be determined. Of 30 patients enrolled in a previous 2-year study,\textsuperscript{8} 27 have continued rituximab treatment for up to 7 years. We present here the updated results of long-term rituximab treatment in the same cohort.

**Methods**

**Patients**

The original study cohort included 30 patients with NMOSD; inclusion criteria have been described in detail elsewhere.\textsuperscript{8} In brief, patients were required to have (1) a diagnosis of NMO (according to the 2006 diagnostic criteria)\textsuperscript{9} or NMOSD\textsuperscript{10} and (2) at least 1 relapse during the 12 months before the start of rituximab therapy. Treatment protocols were approved by the institutional review board of the National Cancer Center.

**Treatment Protocol**

The treatment protocol of the initial 2-year study included induction and maintenance phases. Two regimens were used as induction treatment: (1) 375 mg/m\textsuperscript{2} infused once weekly for 4 weeks (n = 16) and (2) 1000 mg infused twice at a 2-week interval (n = 14). Peripheral blood samples were obtained every 6 weeks throughout the first year and every 8 weeks throughout the second year to evaluate lymphocyte subsets, including CD27\textsuperscript{+} memory B cells and anti-AQP4 antibody levels. The therapeutic target for CD27\textsuperscript{+} memory B-cell depletion was defined as less than 0.05% in peripheral blood mononuclear cells (PBMCs), and patients were given 1 additional infusion of rituximab (375 mg/m\textsuperscript{2}) when the memory B-cell frequency was at least 0.05% in PBMCs. After completion of the initial 2-year study, the interval for monitoring memory B cells was extended to 10 weeks, and patients received 1 additional infusion of rituximab (375 mg/m\textsuperscript{2}) as maintenance therapy whenever the frequency of reemerging memory B cells in PBMCs exceeded 0.1%, as determined by flow cytometry (Figure 1). No patient was given concomitant immunosuppressants while receiving rituximab.

**Clinical Assessment**

The primary end point was the annualized relapse rate (ARR) for each patient, and the secondary end points were neurological status, as indicated by the Expanded Disability Status Scale (EDSS) score, and the safety of rituximab. Relapses were defined as the objective worsening of new neurological symptoms lasting at least 24 hours that increased the EDSS score by at least half a step (0.5). Acute relapses were treated with high-dose intravenous methylprednisolone sodium succinate. If a severe disability persisted after corticosteroid therapy, plasma exchange was performed. Clinical adverse events were recorded throughout the study. Serum levels of IgG were evaluated at baseline and every year thereafter. Serum levels of IgM and IgA were measured every year after 3 years of treatment.

**Flow Cytometric Analysis and Measurement of Serum Anti-AQP4 Antibody Levels**

Simple whole-blood staining was used to characterize leucocyte and B-cell subsets directly from the circulation. Triple-color immunofluorescent staining of whole-blood samples was performed within 60 minutes after blood was collected, using antibodies directed against CD14/CD3/CD19 and CD27/CD19 with isotype controls. This was followed by red blood cell lysis and immediate acquisition and analysis with flow cytometry. The quantitative change in anti-AQP4 antibody levels was measured by using an enzyme-linked immunosorbent assay.\textsuperscript{11}

**Statistical Analysis**

The ARR, EDSS score, and serum anti-AQP4 antibody levels were compared before and after rituximab treatment using the Wilcoxon signed rank test and the 2-sided sign test. Univariate linear regression analyses were used to test for associations among values. All statistical analyses were performed using GraphPad Prism software, version 4.0 (GraphPad), and differences were considered statistically significant at $P < .05$.

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**Figure 1. Treatment Protocol**

Flowchart shows treatment protocol in the current study. IV indicates intravenous; NMO, neuromyelitis optica; NMOSD, NMO spectrum disorder.
Results

Patient Characteristics and Follow-up

Thirty patients (27 women and 3 men) were initially enrolled and treated. The median duration of treatment with rituximab was 60 months (range, 9-82 months). The mean age for starting rituximab therapy was 38 years (range, 23-58 years), and the median interval from the onset of NMO to treatment with rituximab was 4.5 years (range, 0.5-12.9 years). At last review, 27 patients continued re-treatment with rituximab, with a median duration of 61 months (range, 49-82 months). Three patients discontinued rituximab treatment; patient 18 moved to a distant location 2 years after treatment and was unable to visit the clinic, patient 20 switched to mitoxantrone 2 years after starting rituximab because she required too-frequent readministration to maintain therapeutic B-cell depletion, and patient 26 switched to mitoxantrone 9 months after starting rituximab because of sustained relapses during treatment.

Treatment Efficacy

Of the 30 patients, 26 showed a marked reduction in ARR over 5 years (Figure 2). The mean (SD) pretreatment ARR was 2.4 (1.5), and the mean (SD) posttreatment ARR over 5 years was 0.3 (1.0) (P < .001). Eighteen patients (60%) were relapse free during rituximab treatment. Among all patients, the EDSS scores improved in 24 patients and stabilized in 4. 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 (P < .001).

Rituximab Treatment

Over 5 years, the median interval between treatments was 27 weeks (range, 6-68 weeks), and the mean time to re-treatment varied between individuals from 10 to 39 weeks. Subgroup analyses were performed to assess the frequency of re-treatment over 5 years and compare the interval to re-treatment between the first 2 years and thereafter. With the 3 patients who discontinued rituximab excluded from analysis, the mean number of re-treatments after induction was 8 (range, 6-11). The interval until re-treatment with rituximab after 2 years (mean, 36 weeks) was extended compared with that during the initial 2-year study (mean, 23 weeks; P < .001).

Relapses During Treatment

During 5 years, a total of 21 relapses occurred in 11 patients (Table), with 14 occurring in 9 of 30 patients during the initial 2 years and 7 in 4 of 27 patients during the next 3 years. Relapses during the initial 2 years were described in the previous report.8 Five relapses in 5 patients (patients 10, 16, 20, 25, and 27) occurred after induction therapy but before therapeutic depletion, and 3 relapses in 2 patients (patients 11 and 16) occurred in conjunction with delayed re-treatment. Two relapses in 2 patients (patients 9 and 13) occurred despite adherence to the treatment protocol. Two relapses in 2 patients (patients 9 and 29) occurred despite adherence to the treatment protocol, and 4 relapses in 1 patient (patient 26) occurred with incomplete CD27+ memory B-cell depletion despite several re-treatments.8

Among the 7 relapses occurring after the initial 2 years, 2 relapses in 2 patients (patients 7 and 11) occurred in conjunction with delayed re-treatment. Patient 7 missed a scheduled rituximab reinfusion, despite significant reconstitution of memory B cells (0.27%), and experienced relapse 10 weeks after the last memory B-cell assessment. Patient 11 missed a scheduled memory B-cell assessment, which should have been performed 10 weeks after the last assessment, and had a relapse 12 weeks after the last memory B-cell assessment (Figure 3). Five relapses in 2 patients (patients 9 and 29) occurred despite adherence to the treatment protocol. Of note,
during the third year of treatment, patient 9 had 3 relapses during a 6-month period during which the memory B cells were below the 0.05% cutoff. After the fourth relapse during the third year of treatment, a switch in treatment was considered, but the patient refused other immunosuppressants and decided to continue rituximab treatment. No further relapses were observed in the following 2 years of treatment.

### Anti-AQP4 Antibody
Twenty-three patients (77%) were seropositive for the anti-AQP4 antibody. Anti-AQP4 antibody levels were generally reduced or maintained at levels consistent with the initial 2 years of treatment during the follow-up phase. Anti-AQP4 antibody levels gradually increased after 4 years of treatment in conjunction with a prolonged re-treatment interval in 6 patients, but no clinical relapse was observed. Six patients who were initially seropositive were later seronegative at the last follow-up. Seven patients maintained a seronegative status throughout rituximab treatment; 6 were relapse free but 1 (patient 13) had a relapse during the first 2 years. Most relapses were accompanied by an elevation of anti-AQP4 antibody levels, but rising anti-AQP4 antibody levels were not always associated with clinical relapse (Figure 3).

### Flow Cytometric Analysis
With a single readministration of rituximab (375 mg/m²), CD27⁺ memory B-cell frequency decreased to the therapeutic target value in 27 patients. Reconstitution of B cells involves mainly CD27⁻-naive B cells. The median percentage of CD27⁻-naive B cells in the reconstitution of B cells was 86.2% (range, 0.04%–99.6%). Reconstitution of B cells is not necessarily proportional to CD27⁺ memory B cells, and the reemergence of memory B cells above the therapeutic target occurred even in CD19⁺ B cells at less than 0.1% of PBMCs (Figure 4). No relapses occurred in patients with CD27⁺ memory B-cell frequency below the therapeutic target except in patient 9, but 12 (60%) and 13 (65%) of 20 relapses occurred in patients with CD19⁺ B-cell counts less than 0.01 × 10⁹/L or less than 0.5% of PBMCs, respectively, which was considered B-cell depletion in prior studies.

### Safety
Over the 5 years, no case of progressive multifocal leukoencephalopathy or malignancy was observed, and there were no serious adverse events leading to discontinuation of treatment. At last follow-up, serum IgM levels were below the lower limit of normal in 11 (37%) of the patients, IgA levels were low

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### Table. Characteristics of 21 Relapses in 11 Patients During Rituximab Treatment

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Relapse No.</th>
<th>Interval to Relapse, wk</th>
<th>Frequency of CD27⁺ Memory B Cells in PBMCs at Last Analysis Before Relapse, %</th>
<th>Frequency of CD19⁺ B Cells in PBMCs at Relapse, %</th>
<th>CD19⁺ B-Cell Count in Peripheral Blood at Relapse, ×10⁹/L</th>
<th>Frequency of CD27⁺ Memory B Cells in PBMCs at Relapse, %</th>
<th>Anti-AQP4 Antibody Level at Relapse, SU</th>
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**Abbreviations:** AQP4, aquaporin 4; NA, not available; PBMCs, peripheral blood mononuclear cells; SU, standard unit.

⁺ The patient missed a scheduled reinfection despite reconstitution of memory B cells.

**Significant reconstitution of memory B cells because the patient missed a scheduled memory B-cell assessment.**

**Incomplete depletion of memory B cells despite induction treatment or reinfusion of rituximab.**

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Figure 3. Clinical Response, CD27⁺ Memory B Cells, and Anti–Aquaporin 4 Antibody Levels During Rituximab Treatment

Graphs display relationships among clinical response, frequency of CD27⁺ memory B cells, and anti-aquaporin 4 (AQP4) antibody levels during rituximab treatment. SU indicates standard unit.
in 9 (30%), and IgG levels were low in 4 (13%). The most commonly reported infections were respiratory tract infections, urinary tract infections, and a single case of herpes zoster infection, but no serious infections occurred that required treatment with intravenous anti-infective agents. Infusion-related adverse events were noted in 40% of patients during the year after first rituximab exposure but declined in the second year and generally remained stable thereafter.

Discussion

The current study demonstrates the sustained clinical efficacy of repeated rituximab treatment, with no new adverse events during a median 5-year follow-up in patients with NMOSD. Of the 30 patients, 26 (87%) maintained a marked reduction in ARR, and the disability either improved or stabilized in 93% of patients. Over 5 years, 60% of patients were completely free from relapse.

Rituximab is very expensive, and the long-term safety of repeated rituximab treatment is unclear. Any effective treatment strategy that minimizes unnecessary exposure to the drug and allows significant cost savings and safety would be beneficial. We postulated that after the disease activity stabilized, less frequent re-treatment than during the early stage of treatment might be sufficient to prevent a relapse in NMO. Based on our hypothesis, we extended the testing interval and increased the therapeutic threshold of CD27+ memory B cells after completion of the initial 2-year treatment. This might encourage patients to adhere to our strategy during their long-term treatment. Control of disease activity was maintained in 93% of patients. Over 5 years, 60% of patients were completely free from relapse.

Long-term B-cell depletion after repeated rituximab treatment did not give rise to any increased safety risk. Decreases in immunoglobulin levels were observed in some patients after rituximab treatment, but the clinical consequences of these decreases are unclear. The safety profile in the current analysis was consistent with that reported in the patients with rheumatoid arthritis (RA). A recent long-term safety analysis of all clinical trials in patients with RA (3194 patients with 11962 patient-years of observation) found no evidence of an increased safety risk over time or increased reporting rates of any types of adverse events with prolonged exposure to rituximab during up to 9½ years of observation.

To date, the clinical challenges associated with the use of rituximab in patients with NMO are based on developing a re-treatment strategy. In the current study, CD27+ memory B cells in PBMCs were regularly monitored, and re-treatments were adjusted to sustain the therapeutic depletion of these cells. Consequently, a median of 8 single infusions of rituximab (375 mg/m²) after induction were required to prevent exacerbation of disability over 5 years. The cumulative dose in this group is much lower than achieved with the common practice of 4 infusions (375 mg/m²) or 2 infusions (1000 mg) of rituximab at a fixed interval of every 6 to 9 months. This has considerable economic implications. For example, in Korea, the average annual cost of maintenance rituximab therapy for this protocol is lower than the annual cost of the immunosuppressant mycophenolate mofetil. A lower cumulative dose may also decrease the risk of serious adverse effects, such as infection and malignancy. Our findings suggest that tighter control of disease activity by sustaining a predefined therapeutic target before disease activity flares up can enable control of the disease activity with a lower dose. However, confirmation of our observations will require study of a larger cohort using a randomized clinical design to compare our tighter control strategy based on memory B-cell frequencies and fixed 1000-mg dose re-treatment every 6 to 12 months.

The current rituximab protocol with a therapeutic target for memory B-cell depletion is consistent with a recently changed strategy for rituximab treatment in RA. In initial studies with RA, subsequent cycles of rituximab treatment were administered based on clinical disease activity, as needed. However, recent guidelines for RA treatment have advocated a treatment-to-target approach, a treatment strategy tailored to the individual patient whereby patients are regularly monitored and treatment is adjusted to achieve a predefined level of disease activity. In NMOSD, the symptoms of relapse do not present gradually as in RA and there is no defined tool to monitor disease activity. We defined depletion of memory B cells as a therapeutic target representing low disease activity or clinical remission, and treatment was adjusted to achieve a predefined therapeutic target. Thus, our strategy and recent guidelines for treating RA emphasize the importance of keeping disease activity low by applying preemptive re-treatment based on a quantitative therapeutic target.

Previous studies monitored CD19+ B cells in PBMCs to guide treatment decisions, but no specific threshold value was used to determine the timing of re-treatment. In the current study, more than half of relapses occurred at CD19+ B-cell counts below $0.01 \times 10^9/L$ or less than 0.5% of PBMCs but above the therapeutic threshold for CD27+ memory B cells.
whereas no relapses occurred below the therapeutic threshold except in 1 patient. Most important, the reemergence of CD27+ memory B cells above the therapeutic target could occur even with a very small reconstitution of CD19+ B cells (Figure 4). Memory B cells, precursors of autoantibody-producing plasma cells, can elicit rapid and robust responses compared with corresponding antigen-inexperienced naïve B cells.20 Thus, it seems likely that targeting CD27+ memory B cells rather than CD19+ B cells provides a better measure of rituximab efficacy. Over 5 years of rituximab treatment, the overall level of anti-AQP4 antibody was decreased or maintained, but the relationship between clinical outcome and level of anti-AQP4 antibody is less clear than with memory B cells.

The therapeutic target value of 0.05% CD27+ memory B cells in PBMCs was arbitrary, based on our experience before this study. Nevertheless, our current results suggest the relevance of this value as a quantitative threshold to determine re-treatment. All but 1 patient experienced relapses after the reemergence of memory B cells above the defined therapeutic depletion status. In addition, re-treatment after significant repletion of CD27+ memory B cells could not prevent a clinical relapse in patient 16 (Table). This result suggests that additional depletion of CD27+ memory B cells must occur before disease activity increases. Nevertheless, 1 patient (patient 9) had 3 relapses before the proportion of CD27+ memory B cells in PBMCs reached 0.05%. The explanation for this observation is unclear. Although the CD27 marker has been used to represent human memory B cells, recently appearing memory B cells could be further fractionated based on the expression of IgD, IgM, and CD27 as IgM+IgD−CD27+ memory B cells, IgM-only memory B cells, IgD-only memory B cells, IgM−IgD−CD27− memory B cells (class-switched CD27+ memory B cells), and IgM+IgD−CD27+ memory B cells (class-switched CD27− memory B cells).21 Recent studies in patients with RA suggest that baseline blood levels of the molecular marker for late-stage B-cell lineage plasmablasts identify patients who are unlikely to gain substantial clinical benefit from rituximab therapy.22 The re-treatment decision based on more segmented memory B-cell and plasmablast monitoring may elevate the therapeutic efficacy of rituximab in patients with NMO.

Our study was limited by its retrospective analysis, the small number of patients, and the absence of a control group. Moreover, the improvement in EDSS scores may be attributable to recovery from a relapse because the pretreatment EDSS score may have been determined before complete recovery. These limitations notwithstanding, considering the rarity of the disease, the limited evidence of rituximab treatment in NMO, and the ethical difficulties in conducting randomized clinical trials, our results are encouraging and should reassure clinicians regarding the long-term efficacy and safety of rituximab in NMO. Furthermore, this treatment-to-target approach with monitoring of blood memory B cells may enable cost-effective and personalized therapy.

**REFERENCES**


