Placebo-Controlled Trial of Rituximab in IgM Anti–Myelin-Associated Glycoprotein Antibody Demyelinating Neuropathy

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Objective: Report a double-blind, placebo-controlled study of rituximab in patients with anti–MAG demyelinating polyneuropathy (A-MAG-DP).

Methods: Twenty-six patients were randomized to four weekly infusions of 375mg/m^2 rituximab or placebo. Sample size was calculated to detect changes of ≥1 Inflammatory Neuropathy Course and Treatment (INCAT) leg disability scores at month 8. IgM levels, anti-MAG titers, B cells, antigen-presenting cells, and immunoregulatory T cells were monitored every 2 months.

Results: Thirteen A-MAG-DP patients were randomized to rituximab and 13 to placebo. Randomization was balanced for age, electrophysiology, disease duration, disability scores, and baseline B cells. After 8 months, by intention to treat, 4 of 13 rituximab-treated patients improved by ≥1 INCAT score compared with 0 of 13 patients taking placebo ($p = 0.096$). Excluding one rituximab-randomized patient who had normal INCAT score at entry, and thus could not improve, the results were significant ($p = 0.036$). The time to 10m walk was significantly reduced in the rituximab group ($p = 0.042$) (intention to treat). Clinically, walking improved in 7 of 13 rituximab-treated patients. At month 8, IgM was reduced by 34% and anti-MAG titers by 50%. $CD25^+CD4^+Foxp3^+$ regulatory cells significantly increased by month 8. The most improved patients were those with high anti-MAG titers and most severe sensory deficits at baseline.

Interpretation: Rituximab is the first drug that improves some patients with A-MAG-DP in a controlled study. The benefit may be exerted by reducing the putative pathogenic antibodies or by inducing immunoregulatory T cells. The results warrant confirmation with a larger trial.

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Demyelinating polyneuropathy associated with IgM monoclonal gammopathy with antibodies against myelin-associated glycoprotein (MAG) is a distinct entity that presents with progressive sensory ataxia or sensorimotor deficits.[1–6] A causative link between the neuropathy and the MAG antibodies has been proposed based on the following: (1) deposits of IgM and complement on myelin sheaths; (2) widening of the myelin lamellae at the intraperiod line associated with IgM deposition; (3) reproduction of the human pathology after intraneural injection of IgM in rabbits or after systemic infusion of anti-MAG antibodies in chicken; and (4) recognition by the IgM of a carbohydrate MAG epitope, which is shared with a number of other glycoconjugates implicated in cell adhesion, including Po glycoprotein of myelin, Peripheral Myelim Protein-22, (PMP-22), Sulfated Sphingoglycolipid (SGPG), and other related glycolipids.[7–11] Antibodies against SGPG and other glycolipids may inhibit adhesion or neurotransmitter release in experimental animals and block axonal conduction.[2,4,7]

Despite the obvious autoimmune mechanisms underlying this illness, all the available immunotherapies have not been successful. Cyclophosphamide, intravenous immunoglobulin, prednisone, and other immunosuppressants offer only minimal and transient benefit to a small number of them.[12–14] Although in some patients the disease progresses slowly, the majority of patients experience development of significant disability, necessitating the need for exploration of effective therapies.

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against CD20, a protein found on the surface of normal and

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malignant pre-B and mature B cells, until their differentiation into plasma cells.[15,16] The drug, approved for the treatment of refractory B-cell dyscrasias and follicular B-cell lymphomas, results in a rapid and sustained depletion of circulating and tissue-based B cells.[17–19] Rituximab is promising in the treatment of several autoimmune diseases and has been approved for the treatment of rheumatoid arthritis.[20] In uncontrolled small series, rituximab improved the symptoms of some patients with IgM anti-MAG demyelinating neuropathy.[21–23] Although the patient sample size was small, long-lasting improvement of the neuropathic symptoms was noted in several of the patients, without adverse effects or infections. These encouraging results prompted us to conduct a double-blind, placebo-controlled study.

Patients and Methods

Patients were selected if they had clinical and electrophysiological evidence of a demyelinating neuropathy, a benign IgM monoclonal spike, and anti-MAG/SGPG antibodies. Patients should not have received any immunosuppressive therapy for at least 6 months before enrollment. At entry, all studied patients should have impaired function as evidenced by affected balance, coordination, frequent falls, or muscle weakness, reflected in ≥ 1 Inflammatory Neuropathy Course and Treatment (INCAT) disability score.

The study was conducted at the National Institutes of Health under a Cooperative Research and Development Agreement between National Institute of Neurological Disorders and Stroke and Genetech. The trial was registered at ClinicalTrials.gov (ClinicalTrials.gov number NCT00050245), and was conducted under a protocol approved by the National Institute of Neurological Disorders and Stroke institutional review board and after granting an Investigational New Drug (IND) to the principal investigator (M.C.D.) from the Food and Drug Administration. Before infusions, the patients had routine blood studies performed, coagulation studies, electrocardiogram and chest radiograph, a panel of autoantibodies including anti-MAG and SGPG, serum IgG, IgA, and IgM, and serum protein electrophoresis with immunofixation electrophoresis. Immunoglobulin levels were monitored every 2 months, and MAG and SGPG titers every 4 months up to a year. Human anti-chimeric antibody titers were assessed at months 2, 6, and 12. After randomization, four weekly intravenous cycles of 375mg/m^2 of rituximab or placebo consisting of a normal saline solution were administered. All patients were admitted to the inpatient unit of the National Institutes of Health Clinical Center under continuous monitoring and following standard safety guidelines. Patients were premedicated with acetaminophen 650mg and diphenhydramine 25mg before infusions. Both drug and placebo were supplied by the National Institutes of Health pharmacy and sent to the floor covered so that all investigators, assessors, evaluators, and nurses remained blinded to the study code. A data and safety monitoring board was established to monitor safety.

Outcome Measures and Analysis

The primary outcome was a change of ≥ 1 point in INCAT disability scale score in the lower extremities at month 8. This is a validated scale used before in inflammatory demyelinating neuropathies including the IgM anti-MAG neuropathy.[24–26] This scale measures leg disability as follows: 0 = walking not affected; 1 = walking is affected but walks independently outdoors; 2 = uses unilateral support (cane, single crutch); 3 = uses bilateral support (cane, crutches); 4 = uses wheelchair but able to stand and walk a few steps with support; and 5 = restricted to wheelchair. The scale was deemed appropriate to capture changes in IgM anti-MAG neuropathy because this neuropathy predominantly affects balance because of sensory ataxia. Scoring was done by the same neurologist for the same patient throughout the study. Secondary measures included assessment of sensory function using the Sensory Neuropathy Sum scale and muscle strength measurements using the Medical Research Council scales, as utilized in other controlled trials.[14] As a "study of opportunity," the median, ulnar, tibial, and peroneal motor and sensory nerve conduction velocities were determined before therapy and at the end of the 12-month follow-up period.[27]

Sample size calculations assumed that untreated patients would either progress at month 8 or remain stable. For the study design, the proportion of patients improving for the untreated control group was set at 0.001, reflecting the assumption of no improvement, and for the treated group at 0.30 based on published data of INCAT scales.[24–26] Sample size determination for a two-sided Fisher exact test with probability of type 1 error set at 0.05 and power 0.80 indicated 13 patients in each group. Comparisons of baseline measurements between the randomized groups used either χ^2 tests, t test, or nonparametric test as appropriate. To track changes over time for various clinical measurements by assigned treatment, we used repeated-measures analysis of variance model with Scheffe adjustments for multiple comparisons.

The changes in the times for the 10m walk between the treatment groups were compared by repeated-measures analysis of variance. Examination-to-examination variability was accounted for by the analysis with the corresponding F-statistic. The Giesser–Greenhouse correction for sphericity was also applied.

In an attempt to identify factors associated with the responders, post hoc comparisons of the improved patients versus the nonimproved ones was performed using Mann–Whitney U tests on the following eight baseline factors: age, disease duration, 10m walk, Medical Research Council scores, sensory scores, IgM levels, B cells, and MAG antibody titers.

At the end of the study and before breaking the study code, the patients were asked the following questions regarding the degree and significance of their improvement, as well as their tolerance to the infusions: (1) Did any of your symptoms improve? (2) How long after the last infusion did you notice a change? (3) How important was the improvement for your daily activities? (4) What specific activities did you become able to perform after the infusions that you could not do before? (5) How long did the improvement last? (6)

How disabling was your neuropathy, on a scale of 1 to 10 (10 being the worst), before and after therapy? and (7) Did you notice any adverse effects after each infusion?

Immunological Studies

Anti-$CD20^+$ peripheral B-cell counts were measured by fluorescence-activated cell sorting analysis at baseline, after 1 month, and on a bimonthly basis up to 12 months. In addition to B-cell counts, the IgM, IgG, and IgA levels, as well as the anti-MAG and SGPG antibody titers, were measured every 4 months. The effect of rituximab on cell-surface immunological markers, including those characteristic for antigen-presenting cells, were determined by three-color flow cytometry (BD FACSCalibur, San Jose, CA). Primary antibodies used for flow cytometry were human leukocyte antigen-D related, CD20, CD22, CD19, CD27, CD40, CD11c, B7-1, B7-2, Induciele costimulator on activated T cells (ICOS) and ICOS-L, CD3, and CD4 (BD Biosciences, San Jose, CA) labeled with fluorescein isothiocyanate, PE, or antigen-presenting cells. Changes in the $CD4^+CD25^+$ regulatory T cells were measured using flow cytometry by intracellular Foxp3 staining, together with cell-surface staining for CD4 and CD25. Foxp3 phycoerythrin (PE), CD4-fluorescein isothiocyanate, and CD3 antigen-presenting cells were obtained from Ebiosciences (San Diego, CA).

Results

Randomization

Twenty-six patients were randomized; 13 to rituximab and 13 to placebo. One patient who experienced development of bronchospasm immediately after the infusion dropped out of the study and was replaced by an additional patient, after institutional review board approval, to meet the preset sample size; this patient entered the study after randomization. Randomization was balanced in between treatment groups regarding age, disease duration, baseline INCAT scores, time to 10m walk, electrophysiology, IgM level, and baseline B-cell count (Table). The only significant difference was the sex, as more men than women were randomized to rituximab.

Clinical Evaluations

At baseline, the average INCAT leg scores were 1.54 ± 1 for the placebo and 1.46 ± 1 for the rituximab group. One patient, randomized to rituximab and properly rated at screening as having an INCAT score of 1, was discovered in retrospect that he had been entered as having a normal (0) INCAT leg score. Because this patient could not have improved based on the definition of response, analyses were conducted both including him (intention to treat [ITT]) and excluding him (efficacy). Among the rituximab-treated patients, four improved by ≥1 INCAT scores after 8 months; in contrast, none of the patients in the placebo group improved and one worsened ($p = 0.096$, Fisher Exact test). When the patient with normal INCAT score at entry was excluded from the analysis because, by definition, he could not improve, the difference between the rituximab and placebo groups was significant (0.036).

Changes in the mean of the INCAT leg scores, used only descriptively because INCAT is a categorical scale, illustrate the direction of the scores between the two treatment groups (Fig 1A). After 8 months, the mean scores for the placebo group were slightly increased from 1.45 ± 0.7 to 1.54 ± 0.07; in contrast, the scores for the rituximab group were reduced from 1.46 ± 1.0 to 1.08 ± 0.67, confirming the benefit of rituximab.

The baseline times for the 10m walk were 9.5 ± 4.2 seconds for the placebo group and 8.3 ± 3.2 seconds

Table. **Baseline and 8-Month Data on Randomization of Patients Who Received Placebo or Rituximab (Means ± Standard Deviations)**

Characteristics	Baseline		8 Months	
	Placebo (n = 13)	Rituximab (n = 13)	Placebo (n = 13)	Rituximab (n = 13)
Mean age ± SD, yr	67.6 ± 8.4	66,8 ± 7.9		
Mean disease duration ± SD, yr	12.9 ± 6.5	12.9 ± 7.2		
Mean INCAT leg score ± SD	1.45 ± 0.7	1.46 ± 1. 0	1.54 ± 0.7	1.00 ± 0.7
Mean 10m walk ± SD seconds	9.53 ± 4.15	8.3 ± 3.2	9.33 ± 4.0	7.4 ± 2.5
Mean MRC Scale score ± SD	131.6 ± 11.2	134.6 ± 11.9	133.8 ± 11.5	137.6 ± 12.9
Mean IgM level ± SD mg/dl	698.5 ± 446	599 ± 526	731.2 ± 463	344.6 ± 166
Mean B cells ± SD	10.3 ± 5.5	10.9 ± 7.0	10.2 ± 5.8	1.5 ± 2.0
Mean sensory scores ± SD	7.9 ± 3.1	7.5 ± 3.6	6.5 ± 2.7	5.6 ± 3.3
Mean MAG level ± SD units/ml	31.7 ± 51.4	38.8 ± 57.5	43.5 ± 54.4	17.4 ± 30.6
Sex, F/M	7/6	2/12		

[a]Shows descriptive changes of severity, as Inflammatory Neuropathy Course and Treatment (INCAT) is an ordinal scale.
SD = standard deviation; MRC = Medical Research Council; MAG = myelin-associated glycoprotein.

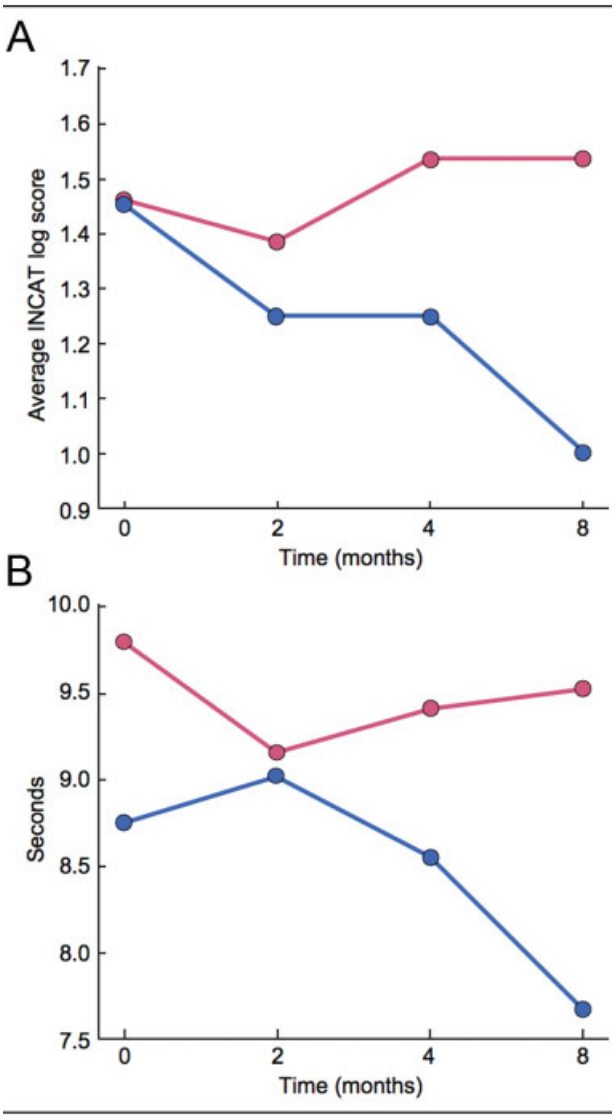

Fig 1. (A) Changes on the Inflammatory Neuropathy Course and Treatment (INCAT) leg scores over time after treatment with rituximab or placebo. An improvement (reduction of INCAT scores) was noted at month 8 for the rituximab group (blue) compared with placebo (red). (B) Difference in the 10m walk time by repeated-measures analysis of variance between the treatment groups. A significantly improved gait was seen in the rituximab group (blue) compared with placebo (p = 0.042) (red) in the intention-to-treat analysis.

for the rituximab group; the corresponding times after 8 months on study were 9.3 ± 3.9 seconds for the placebo group and 7.4 ± 2.5 seconds for the rituximab group, demonstrating significant improvement (p = 0.042) for the ITT analysis (see Fig 1B). Five of 13 placebo-treated patients (38.5%) had improved their time to walk by 0.19 ± 1.3 seconds, compared with 9 of 13 (69.3%) rituximab-treated patients who improved their time to walk by 0.94 ± 1.5 seconds (p = 0.042) (ITT).

Based on clinical assessments and patient questionnaires regarding their motor function and performance, among the 13 placebo-treated patients, 6 had worsened, 7 remained unchanged, and none improved at month 8; in contrast, among the 13 rituximab-treated patients, 1 worsened, 5 remained unchanged, and 7 improved. Three of the improved patients became able to run, play golf, dance or walk unassisted; one, who was using an electric scooter, became independent; and three others experienced better balance, reduced paresthesias or pain, and stopped falling.

No significant changes were noted in the Medical Research Council scales in the rituximab group (see the Table), but this was not unexpected for such a predominantly sensory neuropathy. The mean sensory scores nonsignificantly decreased in the rituximab group (see the Table). No significant changes in the nerve conduction studies, including latencies and amplitudes of the evoked responses, were also noted.

Effect of Rituximab on Serum IgM Level and Anti–Myelin-Associated Glycoprotein Antibodies

The IgM level started to decrease by the second month after treatment (Fig 2A) and was reduced by 34% by

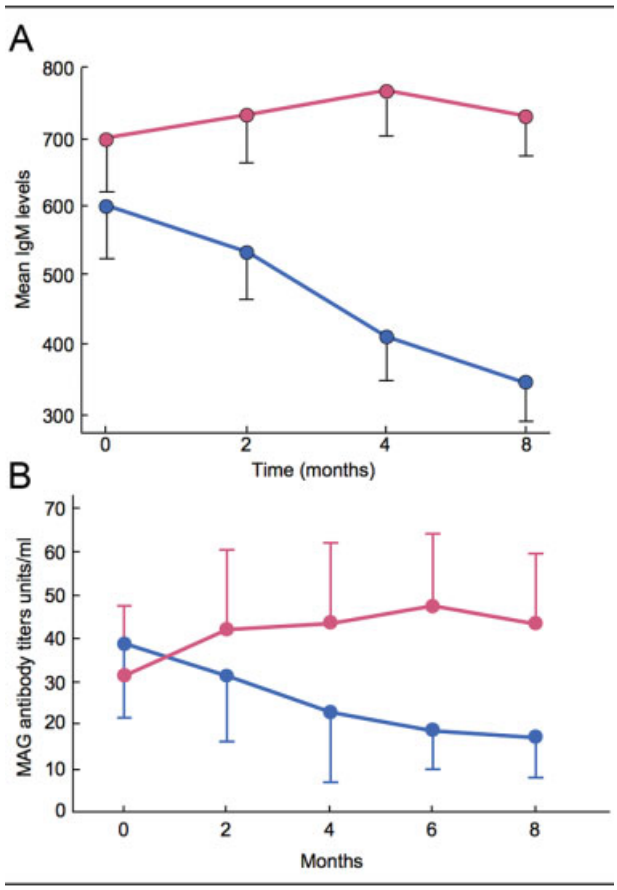

Fig 2. (A, B) Effect of rituximab on IgM levels (A) and anti–myelin-associated glycoprotein antibody titers (B) shows a 34 and 50% reduction, respectively, at month 8. Rituximab = blue; placebo = red.

the eighth month. Similarly, the anti-MAG antibody titers were reduced by 50% at month 8 (see Fig 2B).

Effect on Rituximab on B Cells, B-Cell Repopulation, Costimulatory Molecules, and Immunoregulatory T Cells

As expected, the $CD20^+$ B cells became undetected by the second month after rituximab and remained low till month 6 (Fig 3A). Detectable new B cells were noted at month 8 and increased by month 10 but remained well below the baseline level. The initial B-cell population that emerged and was detected at month 6 after depletion was of the $CD20^+CD19^+CD22^+$ memory phenotype (data not shown). The $CD20^+CD27^+$ memory B cells began emerging at 8 months and remained significantly below baseline up to 12 months (see Fig 3B). There was no effect on CD40, CD40L, ICOS-L, or other markers of antigen-presenting cells other than a slight but significant increase in ICOS-positive cells at 6 months after treatment (data not shown). A significant increase was, however, noted in the $CD4^+CD25^+Foxp3^+$ immunoregulatory cells at month 8 after rituximab compared with placebo ($p < 0.009$) (see Fig 3C). The increased level of these cells became noticeable even at month 4, but at this time the change was not significant ($p < 0.06$).

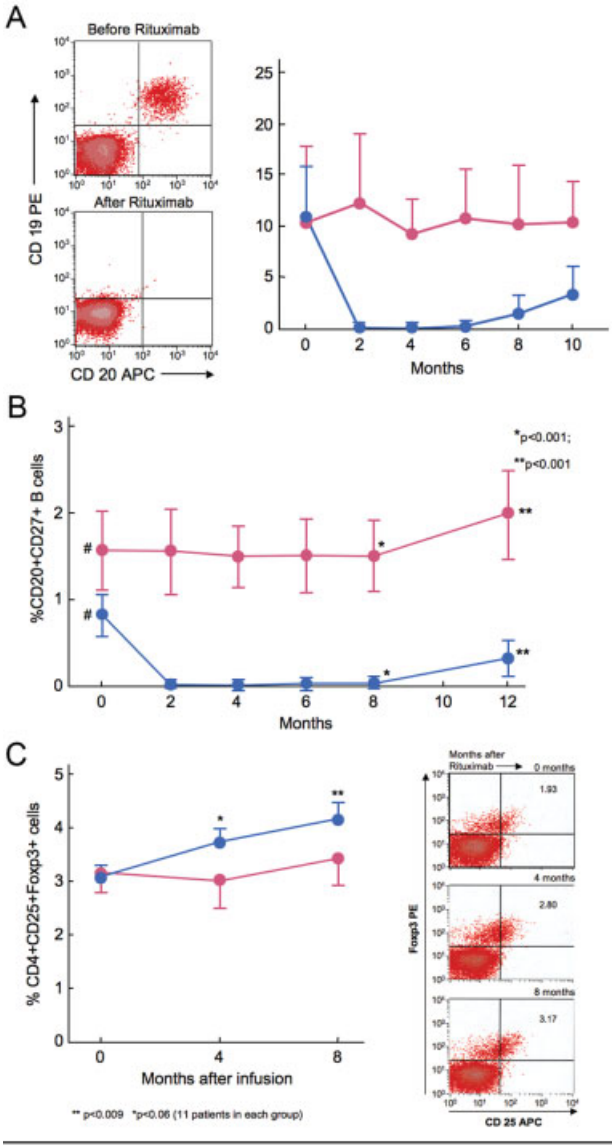

*Fig 3. Effect of rituximab on $CD20^+$ B cells (A) and $CD20^+CD27^+$ memory B cells (B) shows an immediate depletion that lasts 6 to 8 months. Repopulation of the memory B cells starts a little later, at month 8, and remains still low at month 12. The emergence of $CD4^+CD25^+Foxp3^+$ immunoregulatory T cells started slowly to appear at month 4 with a significant increase at month 8 (C). Placebo = red; rituximab = blue. APC = antigen-presenting cell. (B) *p < 0.01; **p < 0.01. (D) *p < 0.06 (n = 11); **p < 0.009 (n = 11).*

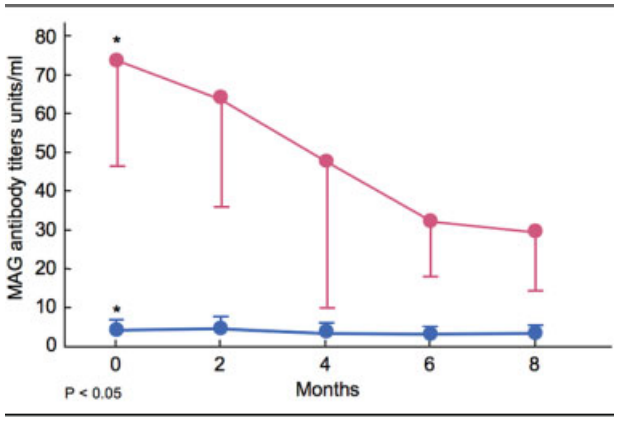

*Fig 4. A relation between titers of anti–myelin-associated glycoprotein (MAG) antibody at baseline and clinical response was observed at month 8. The nonresponders had low baseline anti-MAG antibody titers. Nonresponders = blue; responders = red. *p < 0.05.*

Factors Associated with Clinical Response

Post hoc analysis showed a relation between the subset of patients who responded to rituximab and their baseline level of IgM anti-MAG antibody titers. As shown in Figure 4, the patients with low MAG titers at baseline (even thought they had high SGPG titers) did not respond; in contrast, the baseline MAG titers in the responders were high and decreased from a mean of 40 to 20 units at month 8, suggesting that high anti-MAG titers may determine treatment susceptibility. No such relation was noted with the anti-SGPG antibody titers.

The sensory sum score was also greater in the improved patients (10.8 ± 1.8) compared with those who did not respond (6.0 ± 3.2), with a $p = 0.02$, suggesting that patients with more severe sensory impair-

ment appear more likely to respond. No other associations were noted.

Adverse Effects

The drug was well tolerated. The noted infusion-related reactions were equally balanced in both groups. Specifically, mild temperature increase with chills was noted in three rituximab and one placebo-infused patient, headaches and mild hypotension were noted in two rituximab-treated patients, nausea was observed in two rituximab and two placebo-receiving patients, and vomiting occurred in one patient receiving placebo. One patient taking placebo experienced development of herpes zoster. Dizziness and lightheadedness were observed in one rituximab and one placebo-infused patient; itching was noted in two rituximab- and one placebo-treated patients, and erythematous rash developed in one rituximab- and two placebo-treated patients. One patient taking rituximab experienced development of bronchospasm and was removed immediately after the infusion began.

Discussion

This is the first randomized, controlled trial in anti-MAG demyelinating neuropathy patients that shows a benefit favoring treatment with rituximab. Although the ITT analysis did not reach significance ($p = 0.96$) because one rituximab-randomized patient was rated as having normal INCAT score at entry, when this patient was not included in the analysis because he could not improve, the study showed significant improvement of rituximab compared with placebo ($p = 0.036$). Improvement was measured by the INCAT scale, which was deemed sensitive to capture clinically meaningful changes in leg disability caused by autoimmune neuropathies.[24–26] Four of 13 (31%) rituximab-treated patients improved, whereas 0% improved on placebo and one worsened ($p = 0.036$). The improvement was corroborated with the time-to-walk assessment, which demonstrated a significant functional improvement in the rituximab-treated patients compared with placebo, based on the ITT analysis.

A Cochrane review has concluded that results from available trials do not provide evidence to recommend any immunotherapy in this neuropathy,[28] as none of the available agents is effective. The disease predictably leads to functional impairment and significant disability, from mild distal weakness and unsteadiness to wheelchair confinement. Although 31% of the patients improved based on the INCAT scales, time to walk increased in up to 69% ($p = 0.042$) of the patients. Furthermore, clinical evaluations, including the patients' own assessments before breaking the study code, showed that up to 50% of the rituximab-treated patients were able to walk unassisted, had better balance, became able to run, play golf, had a lesser number of falls or reduced pain, and increased their daily activities for the first time in years. The noted discrepancy between INCAT and functional performance suggests that INCAT is not a sensitive scale to capture small changes in patients' functions especially in the range between 0 and 1, where the functional changes cannot be quantified. It is likely, therefore, that the changes captured with the INCAT scale are on the conservative side and the drug's efficacy might have been underestimated.

Rituximab caused depletion of B cells lasting for more than 6 to 8 months and resulted in reduction of IgM level by 34% and the MAG titers by 50%. Although the onset and peak of improvement coincided with B-cell depletion, it is unclear whether the improvement was due to depletion of B cells or to reduction of autoantibodies. The noted relation between mean baseline MAG titers and clinical response suggests that MAG may be a critical factor in the disease pathogenesis and the anti-MAG antibody titers may be of value in predicting the responders. This information strengthens the pathogenic role of MAG antibodies in the neuropathy but needs to be confirmed in larger series. Because an induction of $CD4^+$ $CD25^+foxp3^+$ regulatory T cells was also observed and coincided with the onset of clinical response, it is conceivable that these cells might have played a critical role in suppressing the immune response. The induction of $CD4^+CD25^+$ T regulatory cells by rituximab is a novel observation and warrants further investigation in exploring the mechanisms of action of the drug in autoimmune disorders.

A surprising observation with this immunotherapy was the long-lasting remission of the response. In most patients, the improvement began after 3 months; it was clear by the sixth month and lasted for up to a year or longer. Although follow-up infusions may be needed to maintain the clinical response in the following years, as noted with rituximab in other disorders,[29,30] the need for repeated infusions was beyond the objective of this study.

It remains unclear why only some of the patients improved with rituximab. Although the sample size was small for accurate predictions, it appears that high anti-MAG antibody titers and the presence of more severe sensory impairments increase the chances to respond. There was no association between improvement and disease duration, age, IgM level, or electrophysiology. The degree of axonal loss, inevitable in all chronic inflammatory demyelinating neuropathies, was not different between the two groups, even though three of the patients who did not respond had a chronic and severe axonal loss. The repeated nerve conduction studies, including the amplitudes of the nerve action potentials, did not appreciably change after therapy, confirming that routine electrophysiology is not sensitive

enough to capture small but clinically meaningful changes in the regenerated large axons. Similar observations were recently made in patients with chronic demyelinating polyneuropathy who responded to intravenous immunoglobulin.[26]

Changes in the levels of the circulating IgM antibodies or immunoglobulins, produced by the CD20-positive plasma cells, was not expected to occur after rituximab. However, reductions up to twofold to threefold in IgM antibody titers have been noted in previous studies not only in neuropathies but also in rheumatoid arthritis.[20–23,30,31] This is probably due to depletion of $CD27^+$ memory B cells, the precursors of the short-lived plasma cells, as demonstrated in our study. As the $CD27^+$ memory B cells reappear, so do the short-lived plasma cells.[30] The antibody titers therefore may decline after rituximab treatment and rebound slowly at a rate controlled by the replenishment of memory and short-lived plasma cells.[30–32] Whether this effect relates to the beneficial effect of rituximab in anti-MAG-related neuropathies is unclear. It is intriguing, however, to note that the onset and peak of improvement appear to correspond with the reduction of IgM level and antibody titers (see Figs 1–3), suggesting that B-cell factors (antibodies, cytokines) may play a role in initiating improvement before axonal regeneration takes place.

Rituximab was well tolerated. None of the infusion-related mild reactions or side effects was obviously distinct between rituximab and placebo to unblind the observers among the patients who completed the infusions. Similar observations were made recently in a large trial of rituximab in multiple sclerosis patients.[33] Most importantly, despite the B-cell depletion, no impairment of clinical immunity or signs of opportunistic infections were noted as recently emphasized,[32] although a recent Food and Drug Administration warning about the possibility of Progressive Multifocal Leucoencephalopathy (PML) when rituximab is combined with other drugs should be taken into consideration.[34] The results from this controlled clinical trial are encouraging for such a treatment-resistant neuropathy and warrant further studies with a larger patient sample.

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