Placebo-controlled trial of rituximab in IgM anti-myelin–associated glycoprotein neuropathy

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ABSTRACT

Objective: To determine whether rituximab 375 mg/m² was efficacious in patients with immunoglobulin M (IgM) anti-myelin-associated glycoprotein antibody demyelinating neuropathy (IgM anti-MAG demyelinating neuropathy).

Methods: Fifty-four patients with IgM anti-MAG demyelinating neuropathy were enrolled in this randomized, double-blind, placebo-controlled trial. The inclusion criteria were inflammatory neuropathy cause and treatment (INCAT) sensory score (ISS) ≥ 4 and visual analog pain scale > 4 or ataxia score ≥ 2 . The primary outcome was mean change in ISS at 12 months.

Results: Twenty-six patients were randomized to a group receiving 4 weekly infusions of 375 mg/m² rituximab, and 28 patients to placebo. Intention-to-treat analysis, with imputation of missing ISS values by the last observation carried forward method, showed a lack of mean change in ISS at 12 months, 1.0 ± 2.7 in the rituximab group, and 1.0 ± 2.8 in the placebo group. However, changes were observed, in per protocol analysis at 12 months, for the number of patients with an improvement of at least 2 points in the INCAT disability scale ($p = 0.027$), the self-evaluation scale ($p = 0.016$), and 2 subscores of the Short Form-36 questionnaire.

Conclusions: Although primary outcome measures provide no evidence to support the use of rituximab in IgM anti-MAG demyelinating neuropathy, there were improvements in several secondary outcomes in per protocol analysis.

Level of evidence: This study provides Class I evidence that rituximab is ineffective in improving ISS in patients with IgM anti-MAG demyelinating neuropathy. *Neurology*® 2013;80:2217-2225

GLOSSARY

AE = adverse events; **BAFF** = B-cell-activating factor; **IgM** = immunoglobulin M; **INCAT** = inflammatory neuropathy cause and treatment; **ISS** = inflammatory neuropathy cause and treatment sensory score; **MAG** = myelin-associated glycoprotein; **RCT** = randomized controlled trial; **RIMAG** = Rituximab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy; **SF-36** = Short Form-36; **UFRCB** = Unit of Clinical Research and Biostatistics; **VAS** = visual analog pain scale.

Within the spectrum of chronic immune-mediated neuropathies, demyelinating neuropathy associated with immunoglobulin M (IgM) monoclonal gammopathy and antibodies against myelin-associated glycoprotein (MAG) is a distinct entity that typically presents with progressive sensory ataxia and painful paresthesias.¹⁻⁸ Patients present with a striking immunochemical profile, suggesting the possibility of an autoimmune mechanism: monoclonal IgM recognizes a carbohydrate MAG epitope, which is shared with a number of other glycoconjugates involved in cell adhesion, including the Po glycoprotein of myelin, peripheral myelin protein-22, sulfated sphingolipid, and other related glycolipids.^{9,10} The disease may progress slowly over many years in some patients, whereas others develop significant disability mostly due to dysesthesias and ataxia; thus, there is a need to develop effective treatments.¹¹

Supplemental data at
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There is insufficient evidence from most pilot studies or randomized controlled trials (RCT) on IgM anti-MAG demyelinating neuropathy to recommend any particular immunotherapy.^{12,13} Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against CD20, a protein present on the surface of normal and malignant pre-B and mature B cells until differentiation into plasma cells. Efficacy of rituximab has been supported by both uncontrolled studies^{14–17} and, more recently, an RCT that concluded there was a small difference between rituximab and placebo-treated patients,¹⁸ although confirmation is needed in a larger trial. The aim of the Rituximab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy (RIMAG) study was to test the hypothesis that rituximab at 375 mg/m² is beneficial in patients with IgM anti-MAG demyelinating neuropathy.

METHODS **Participants.** Patients, aged 18 to 82 years, were enrolled at 8 neuromuscular centers in France and one in Switzerland between March 2006 and November 2008. Inclusion and exclusion criteria are listed in table 1. Criteria for chronic demyelinating neuropathy accorded with the European Federation of Neurological Societies/Peripheral Nerve Society guidelines for chronic inflammatory demyelinating polyradiculoneuropathy.¹⁹

Using a stratified (by center) and blocked (with variable block length) randomization list (created by a statistician) to ensure that the 2 parallel groups were comparable at baseline, patients were randomized by fax to one of two groups (1:1 ratio): the first group received 4 weekly infusions of 375 mg/m² rituximab (as in regimens used in previous trials for IgM anti-MAG demyelinating neuropathy¹⁸) and the second group received placebo. Randomization was centralized and carried out independently of the clinicians. Once randomized, the patients were allowed no other immunomodulatory or immunosuppressive treatment until they reached the predefined endpoints. The study included a treatment period (weeks 1–4) and a follow-up period (week 4–month 12). Patients were assessed at baseline, and at 3, 6, 9, and 12 months, but early assessment took place if clinically necessary (e.g., due to a worsening of the patient's condition). Drug and placebo were supplied by Roche France. All investigators, assessors, evaluators, and nurses remained blinded to the randomization codes. A data and safety monitoring board was established to monitor safety.

Standard protocol approvals, registrations, and patient consents. All patients provided written informed consent. The ethics committees of all participating centers approved the study protocol. This study was registered with Current Controlled Trials, under number 00259974, and was investigator-led and cosponsored by Assistance Publique-Hôpitaux de Paris (Direction de la Recherche Clinique), with financial support from a Programme Hospitalier de Recherche Clinique grant (PHRC no 04049 obtained from the French Ministry of Health in 2004).

Outcomes. The primary outcome was the absolute change in inflammatory neuropathy cause and treatment (INCAT) sensory

Table 1 Inclusion and exclusion criteria: Rituximab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy (RIMAG) study

Inclusion criteria
Chronic demyelinating neuropathy according to the European Federation of Neurological Societies/Peripheral Nerve Society guidelines for chronic inflammatory demyelinating polyneuropathy
Immunoglobulin M monoclonal antibody peak
Immunoglobulin M anti-myelin-associated glycoprotein antibody titers >1,000 Bühlmann titer units
Inflammatory neuropathy cause and treatment sensory score ≥4
Visual analog pain scale >4 and/or ataxia score ≥2
Exclusion criteria
Diseases known to cause neuropathy (e.g., diabetes mellitus, thyroid disease, vitamin B1 or B12 deficiency, or significant hematologic [mostly cryoglobulinemia, myeloma, and amyloidosis], renal, or liver disorders)
Severe comorbidity
Another immunosuppressive therapy in the last 3 months
Previous treatment with rituximab
Known hypersensitivity to rituximab
White blood cell count <1,500 per mm ³ or platelet count <75,000 per mm ³
Patients needing specific immunosuppressive therapy for the hematologic conditions

score (ISS)²⁰ between baseline and month 12 (chosen as an appropriate interval to capture clinical changes), calculated as the sum of evaluation of pinprick sensation on the most affected site on the upper (0–4) and lower (0–4) limbs; evaluation of the vibration generated by a Rydel-Seiffer graduated tuning fork; and evaluation of 2-point discrimination by the index finger. ISS results range from 0 (normal sensation) to 20 (the most severe sensory deficit).

Clinical secondary outcomes considered were relative change in ISS (vs baseline), the number of subjects displaying a 2-point and a 4-point improvement in ISS, and median change in ISS in the legs only. Other secondary clinical outcomes are listed in table 2. Biological secondary outcome measures considered were changes in the number of B cells, CD20 subcount, and anti-MAG antibody titers.

Assessments. Clinical measurements used were ISS, INCAT disability scale (10-point scale, range from 0 = normal to 10 = worst), the sensory component of the neurologic impairment score (possible range 0–32), the Medical Research Council sumscore (0 to 5 for 3 distal muscle groups in 2 upper and 2 lower limbs, range 0–60), time taken to walk 10 meters (in seconds), ataxia score (0 = normal, 1 = slight oscillations, 2 = marked oscillations, 3 = severe ataxia), and visual analog pain scale (VAS) (from 0 = no pain to 10 = maximal pain). A functional score was obtained by asking patients whether they felt that paresthesia, pain, abnormal ground sensation, sensation of constriction, and difficulties in walking had certainly improved = 1, probably improved = 2, remained unchanged = 3, probably worsened = 4, or certainly worsened = 5. For the self-evaluation scale, patients were asked whether treatment improved their neuropathy (1), stabilized their

Table 2 Baseline sociodemographic and clinical characteristics of the patients: Rituximab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy (RIMAG) study

Variable	Analysis population (n = 54)	Placebo group (n = 28)	Rituximab group (n = 26)
Mean age $\pm$ SD, y	66.0 $\pm$ 9.4	67.2 $\pm$ 8.6	64.6 $\pm$ 10.3
Male %	70.4	71.4	69.2
Median disease duration, y (IQR)	3.4 (1.9; 7.0)	3.3 (1.4; 4.8)	3.8 (2.2; 7.9)
Median ISS (IQR)	7.0 (6.0; 9.0)	8.0 (6.0; 10.0)	6.5 (5.0; 9.0)
Median INCAT disability scale score (IQR)	3.0 (2.0; 4.0)	3.0 (2.0; 4.0)	3.0 (2.0; 4.0)
Mean NIS score $\pm$ SD	14.3 $\pm$ 5.2	14.7 $\pm$ 5.0	13.8 $\pm$ 5.6
Median MRC score (IQR)	55.0 (49.0; 60.0)	55.0 (51.5; 60.0)	56.5 (45.0; 60.0)
Median 10-m walk, s (IQR)	9.0 (7.0; 11.6)	9.0 (7.5; 12.1)	7.7 (6.0; 10.7)
Ataxia (2–3), %	70.4	67.9	73.1
Median VAS for pain (IQR)	3.7 (0.8; 6.0)	4.9 (2.2; 6.0)	3.1 (0.2; 6.0)
Mean functional score $\pm$ SD	17.4 $\pm$ 3.0	16.8 $\pm$ 3.1	18.5 $\pm$ 2.9
Median IgM level, g/L (IQR)	3.8 (2.1; 7.2) (n' = 46)	3.8 (3.0; 6.8) (n' = 25)	3.1 (2.0; 7.7) (n' = 21)
Mean monoclonal peak $\pm$ SD, g/L	6.4 $\pm$ 3.7 (n' = 17)	5.7 $\pm$ 2.9 (n' = 7)	6.9 $\pm$ 4.2 (n' = 10)
Median B cells, % (IQR)	9.2 (6.5; 12.5) (n' = 40)	11.5 (6.8; 15.4) (n' = 20)	8.0 (6.5; 10.5) (n' = 20)
Median CD20 cells (IQR)	9.0 (6.0; 12.0) (n' = 35)	9.0 (6.0; 12.0) (n' = 15)	9.0 (5.5; 13.0) (n' = 20)
Median anti-MAG titers (IQR)	$\geq$ 70,000 (26,800; $\geq$ 70,000) (n' = 53)	$\geq$ 70,000 (14,000; $\geq$ 70,000) (n' = 27)	$\geq$ 70,000 (33,000; $\geq$ 70,000) (n' = 26)

Abbreviations: IgM = immunoglobulin M; INCAT = inflammatory neuropathy cause and treatment; IQR = interquartile range; ISS = inflammatory neuropathy cause and treatment sensory score; MAG = myelin-associated glycoprotein; MRC = Medical Research Council; n' = number of available data, when lower than n for the group; NIS = neurologic impairment score; VAS = visual analog scale.

neuropathy (2), or did not prevent neuropathy from worsening (3). Quality of life was evaluated using the Short Form–36 (SF-36) questionnaire.

All patients underwent a full battery of laboratory tests, including immunofixation and monoclonal protein determinations, which were determined by standard procedures. IgM anti-MAG antibodies analyses were all conducted at one laboratory (Department of Immunochemistry, Pitié-Salpêtrière University Hospital, Paris, France), using an ELISA (Bühlmann, Schönenbuch, Switzerland), at 4°C with a 1:1,000 dilution of the patients' serum. The cutoff was 1,000 Bühlmann titer units.

Bone marrow aspirate was obtained from all patients before inclusion to rule out underlying malignant lymphoproliferative disease. Patients also underwent thoracic, abdominal, and pelvic CT scans and skeletal x-ray.

Adverse events were recorded at each visit with a structured questionnaire.

Data collection. Data were collected by each center and implemented in a secured database through an online connection. The database was created, maintained, and validated by the Unit of Clinical Research and Biostatistics (UFRCB) of Limoges University Hospital, France.

Statistical analysis. Sample size. Assuming an α risk of 5% and a β risk of 20%, and considering a worsening of ISS between baseline and 12 months of 10% for patients on placebo and a difference of 20% between patients given rituximab and those given placebo, with an SD of 3.7 for the ISS, we calculated a required sample size of 50 patients. We included 54 patients to account for patients not evaluable at month 12.

Statistical analyses. Personnel from UFRCB conducted statistical analyses using SAS Enterprise Guide software, version 4.3

(SAS Institute, Cary, NC). *p* Values of less than 0.05 were considered statistically significant. Analyses were performed and are presented in accordance with the revised CONSORT statement.²¹

Intention-to-treat analysis was conducted using last observation carried forward imputation of ISS values for subjects withdrawing from the trial before the 12-month (M12) evaluation. In addition, 2 robust analyses with missing data replacement, based on extreme scenarios, were also performed. In scenario 1, subjects from the placebo group not evaluated at M12 were considered to display the largest improvement in ISS between day 0 and month 12 observed in the dataset, while unevaluated subjects in the rituximab group were considered to display the greatest worsening of ISS between day 0 and month 12; in scenario 2, unevaluated subjects at M12 from the placebo group would display the greatest worsening of ISS between day 0 and month 12, whereas unevaluated subjects in the rituximab group would display the largest improvement in ISS between day 0 and month 12. Per protocol analysis was then performed for the main and secondary outcomes.

Means and SDs were determined for quantitative variables following a normal distribution. Medians and interquartile ranges were used for quantitative variables not following a normal distribution. Changes in scores were calculated as follows: absolute change (in score units): difference between values at baseline and at 12 months; relative change (% of change): absolute difference $\times$ 100/value at baseline. Qualitative variables were described as frequencies and percentages. The numbers of missing values were systematically disclosed.

The main analysis was based on the absolute changes in ISS between baseline and 12 months; values were compared using Student *t* tests. Other comparisons of quantitative data were performed with Student *t* tests or Mann-Whitney tests. The Shapiro Wilk test was used to test the distribution of quantitative

variables. Comparisons of percentages were performed with Pearson χ^2 tests or Fisher test, depending on expected frequencies. Scores for the SF-36 quality of life questionnaire were analyzed in accordance with instructions in the user's manual.²²

RESULTS Participants. Between March 2006 and November 2008, 54 patients were randomized as described above and started taking the assigned medication (rituximab or placebo). The last patient completed the study in November 2009. The figure shows a schematic design of the trial. There were 38 men and 16 women; 26 patients were assigned to the rituximab group, and 28 patients to the placebo group. Seven patients withdrew from the trial without subsequent follow-up. One patient from the placebo group withdrew consent at month 3 because he felt no benefit from treatment. Six patients withdrew from the rituximab group, 1 at day 14 and 1 at month 3, citing personal reasons, and 1 at month 3 due to a worsening of clinical condition. One patient withdrew due to side effects on day 1, during the first rituximab infusion (see below), 1 patient was withdrawn due to ECG abnormalities before the first rituximab infusion, and 1 was lost to follow-up at month 6. The population for the intention-to-treat analysis was the total population included in the trial ($n = 54$), whereas per protocol analysis was limited to the population of subjects who completed follow-up ($n = 47$).

Table 2 shows baseline characteristics of the intention-to-treat population. Patients in the 2 groups

were comparable for all demographic and clinical features as well as outcome and biological/immunologic data. The mean age at baseline was 66.0 ± 9.4 years (range 36.5–81.6), and 70.4% of patients were male.

Efficacy. Primary outcome. In the intention-to-treat analysis (table 3; $n = 54$), the change in ISS after 12 months was 1.0 ± 2.7 (range -4 ; 8) for the rituximab group, vs 1.0 ± 2.8 (range -5 ; 8) for the placebo group, which was not a significant difference ($p = 0.92$). This result was confirmed by 2 robust analyses ($n = 54$) based on data imputation in extreme scenarios (scenario 1, $p = 0.18$; scenario 2, $p = 0.07$; Student t test). There was thus no difference in primary outcome between the rituximab and placebo groups.

Secondary outcomes. Other results for ISS were investigated using both intention-to-treat and per protocol analyses (table 3). In both analyses, no change was found.

Results of per protocol analysis for other secondary clinical outcomes are outlined in table 4. Overall, 4 patients (20%) improved at least 2 points on the INCAT disability scale (20% of theoretical maximum) in the rituximab group, and none (0%) in the placebo group ($p = 0.027$).

Analysis of self-evaluation scale data at 12 months revealed the following differences ($p = 0.016$): 5 (26.3%) patients in the rituximab group ($n = 19$) considered their condition improved vs 1 patient

Figure Schematic design of the trial

Table 3 Results for the main analysis (first row) and other analyses of inflammatory neuropathy cause and treatment sensory score in the intention-to-treat population and in the per protocol population: Rituximab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy (RIMAG) study

Variable		Placebo group (n = 28)	Rituximab group (n = 26)	p Value
Intention-to-treat population				
Between day 0 and month 12	Mean change in ISS $\pm$ SD	1.0 $\pm$ 2.8	1.0 $\pm$ 2.7	0.92 ^a
	Mean percent change in ISS $\pm$ SD	10.0 $\pm$ 33.7	11.3 $\pm$ 38.3	0.90 ^a
	ISS improvement $\geq$ 20% with respect to baseline, n (%)	12 (42.9)	11 (42.3)	0.97 ^b
	ISS improvement $\geq$ 4, n (%)	6 (21.4)	4 (15.4)	0.73 ^c
	ISS improvement $\geq$ 2, n (%)	11 (39.3)	8 (34.6)	0.72 ^b
	Median change in ISS for the lower limbs (IQR)	0.0 (−1.0; 1.0)	0.0 (−1.0; 2.0)	0.39 ^d
Variable		Placebo group (n' = 27)	Rituximab group (n' = 20)	p Value
Per protocol population				
Between day 0 and month 12	Mean change in ISS $\pm$ SD	1.0 $\pm$ 2.8	1.3 $\pm$ 3.0	0.68 ^a
	Mean percent change in ISS $\pm$ SD	10.4 $\pm$ 34.3	15.5 $\pm$ 42.2	0.64 ^a
	ISS improvement $\geq$ 20% with respect to baseline, n (%)	12 (44.4)	10 (50.0)	0.77 ^b
	ISS improvement $\geq$ 4, n (%)	6 (22.2)	4 (20.0)	1.00 ^c
	ISS improvement $\geq$ 2, n (%)	11 (40.7)	8 (40.0)	0.95 ^b
	Median change in ISS for the lower limbs (IQR)	0 (−1.0; 1.0)	1.0 (−0.5; 3.0)	0.15 ^d

Abbreviations: IQR = interquartile range; ISS = inflammatory neuropathy cause and treatment sensory score; n' = number of available data when lower than n for the group.

^a Student t test.

^b χ^2 test.

^c Fisher exact test.

^d Mann-Whitney test.

(4%) in the placebo group (n = 25); 10 (52.6%) patients in the rituximab group considered their condition stabilized vs 9 (36%) patients in the placebo group; and 4 (21%) patients in the rituximab group considered their treatment was of no benefit vs 15 (60%) in the placebo group. Absolute changes in SF-36 scores and subscores between baseline and 12 months were mostly not significant, except for the mean changes in physical function and emotional role ($p = 0.006$ and 0.02 , respectively).

Overall, changes were observed in per protocol analysis for INCAT disability scale, self-evaluation scale, and 2 subscores of the SF-36 questionnaire. Differences between baseline and M12 were found for the median change in mean B-cell subcount ($p = 0.002$), change in IgM anti-MAG titers ($p = 0.0015$), and change in CD20+ B-cells subcount ($p = 0.003$) (table 5).

Safety. In total, 62 adverse events (AE) were recorded, evenly distributed between the 2 groups. Twenty-six patients had no AE (14/28 in the placebo and 12/26 in the rituximab groups), whereas 28 had at least one AE (14 in the placebo group and 14 in the rituximab group) ($p = 0.77$). In the rituximab group, 14 patients experiencing AE had only one such event, 5 patients experienced 2, 3 patients experienced 3,

3 patients experienced 4, 2 patients experienced 5, and 1 patient experienced 7 AE. Nine serious AE occurred, including the following: generalized erythematous rash and itching after injection in 2 rituximab patients; bradycardia in 1 rituximab patient and 1 placebo patient (the rituximab patient withdrew because of this AE); diplopia in 1 rituximab patient; dyspnea in 1 rituximab patient; fractured tibia in 1 rituximab patient; anemia in 1 rituximab patient (linked to a hemorrhagic polyp in the left colon); and finally, the rituximab-treated patient who experienced the erythematous rash also complained of dizziness and lightheadedness but with no evidence of a cardiovascular event. Four of these serious AE were classified as independent from the treatment, and the remaining 5 were probably related to treatment.

DISCUSSION This randomized, double-blind, controlled trial in 54 patients with IgM anti-MAG demyelinating neuropathy treated with placebo or rituximab at 375 mg/m² (4 weekly infusions) provided no evidence of improvement in primary outcome measures. Per protocol analysis revealed an improvement in several secondary outcomes. Nevertheless, as 6 patients withdrew from the rituximab group vs 1 in the placebo group, interpretation based on per

Table 4 Results for secondary analysis for clinical evaluation (change from D0 to M12), functional scores (evaluated at M12), and SF-36 scores (change from D0 to M12) in the per protocol population: Rituximab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy (RIMAG) study

Variable	Placebo group (n = 27)	Rituximab group (n = 20)	p Value
Median change in INCAT disability scale score (D0-M12) (IQR)	0.0 (−1.0; 0.0) (n' = 27)	0.0 (−1.0; 1.0) (n' = 20)	0.22 ^a
Improvement in INCAT disability score ≥2, n (%)	0 (0.0)	4 (20.0)	0.027 ^b
Improvement in INCAT disability score ≥1, n (%)	4 (14.8)	8 (40.0)	0.0503 ^c
Mean change in NIS (D0-M12) ± SD	1.8 ± 5.1 (n' = 26)	1.1 ± 6.0 (n' = 19)	0.69 ^d
Median change in MRC score (D0-M12) (IQR)	0.0 (−3.0; 0.0) (n' = 27)	0.0 (−1.5; 1.5) (n' = 20)	0.17 ^a
Mean change in 10-meter walk time, s (D0-M12) ± SD	0.1 ± 2.7 (n' = 24)	0.3 ± 3.2 (n' = 18)	0.84 ^d
Ataxia (2–3), n (%)	17 (65.4) (n' = 26)	13 (65.0) (n' = 20)	0.98 ^c
Mean change in VAS score for pain ± SD	−0.07 ± 1.7 (n' = 24)	0.61 ± 2.3 (n' = 17)	0.28 ^d
Mean functional score at M12 ± SD	14.8 ± 4.3 (n' = 25)	12.0 ± 5.5 (n' = 17)	0.07 ^d
Self-evaluation scale at M12	(n' = 25)	(n' = 19)	0.016 ^b
Improvement, n (%)	1 (4.0)	5 (26.3)	
Stabilization, n (%)	9 (36.0)	10 (52.6)	
No effect, n (%)	15 (60.0)	4 (21.0)	
SF-36 scores, absolute change (D0-M12)			
Physical component summary scales (mean ± SD)	−0.5 ± 4.1 (n' = 15)	3.1 ± 6.6 (n' = 14)	0.08 ^d
Mental component summary scales (mean ± SD)	0.4 ± 9.2 (n' = 15)	3.2 ± 8.9 (n' = 14)	0.41 ^d
SF-36 subscores, absolute change (D0-M12)			
Physical functioning (mean ± SD)	−3.9 ± 9.8 (n' = 20)	11.6 ± 19.6 (n' = 17)	0.0069 ^d
Role-physical (median, IQR)	0.0 (0.0; 25.0) (n' = 23)	0.0 (−25.0; 25.0) (n' = 16)	0.76 ^a
Role-emotional (median, IQR)	0.0 (−33.3; 16.7) (n' = 24)	33.3 (0.0; 66.7) (n' = 18)	0.02 ^a
Mental health (mean ± SD)	−2.1 ± 12.8 (n' = 24)	4.5 ± 9.9 (n' = 17)	0.08 ^d
Vitality (mean ± SD)	−1.4 ± 13.1 (n' = 24)	2.1 ± 13.7 (n' = 18)	0.40 ^d
Social functioning (median, IQR)	0.0 (−31.2; 12.5) (n' = 20)	12.5 (0.0; 12.5) (n' = 18)	0.07 ^a
Bodily pain (median, IQR)	0.0 (−10.5; 9.0) (n' = 23)	9.0 (0.0; 11.0) (n' = 17)	0.09 ^a
General health (median, IQR)	0.0 (−11.0; 8.5) (n' = 24)	5.0 (0.0; 15.0) (n' = 17)	0.12 ^a

Abbreviations: INCAT = inflammatory neuropathy cause and treatment; IQR = interquartile range; n' = number of data available when lower than n for the group; MRC = Medical Research Council; NIS = neurologic impairment score; SF-36 = Short Form-36; VAS = visual analog pain scale.

^a Mann-Whitney test.

^b Fisher exact test.

^c χ^2 test.

^d Student t test.

protocol analysis is of limited value. In a previous trial of 26 patients, intention-to-treat analysis showed improvement after 8 months in 4 out of the 13 rituximab-treated patients and none of the 13 placebo patients

($p = 0.096$).¹⁸ These results excluded one patient randomized to the rituximab group who had a normal INCAT score on inclusion, and could not therefore improve ($p = 0.036$).

Table 5 Results for biological markers in the per protocol population: Rituximab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy (RIMAG) study

Variable	Placebo group (n = 27)	Rituximab group (n = 20)	p Value
Median change in B-cell count (D0-M12), % (IQR)	0.0 (−1.4; 4.0) (n' = 15)	6.0 (3.0; 9.5) (n' = 15)	0.002 ^a
Median change in anti-MAG titer (D0-M12), g/L (IQR) ^b	0 (−9,600; 0) (n' = 23)	13,700 (0; 38,000) (n' = 18)	0.0015 ^a
Median change in CD20 count (D0-M12), % (IQR)	−1.5 (−4.0; 0.0) (n' = 10)	7.0 (2.5; 11.5) (n' = 12)	0.003 ^a

Abbreviations: IQR = interquartile range; MAG = myelin-associated glycoprotein; n' = number of available data.

^a Mann-Whitney test.

^b Calculations carried out with a titer of 70,000 for values of 70,000 or more (censored titer).

A potential limit to the comparison with the results of the Dalakas trial is the choice of the inclusion criteria concerning disability: ISS ≥ 4 and VAS > 4 or ataxia score ≥ 2 in our trial, vs INCAT disability score ≥ 1 in the previous trial. In addition, the disease duration before inclusion was lower in our 2 groups (table 2) than in the previous trial (respectively, 12.9 ± 6.5 years in the placebo group and 12.9 ± 7.2 years in the rituximab group).

Another potential limitation of the present study is the choice of primary endpoint as there is currently no consensus concerning the most valid primary endpoint for IgM anti-MAG demyelinating neuropathy. Dalakas and coworkers¹⁸ used a change of at least one point in INCAT disability scale score for the lower limbs only at month 8. This measure was chosen because the INCAT disability scale has been validated for evaluation of various inflammatory demyelinating neuropathies, including IgM anti-MAG neuropathy.^{23–28}

When developing this protocol, the ISS²⁰ at 12 months was classified as an appropriate primary outcome measure when assessing sensory deficit. Nevertheless, neither intention-to-treat nor per protocol analysis showed any difference in the mean change in ISS between the rituximab and placebo groups, or any difference in the numbers (percentages) of patients displaying an improvement in overall ISS score of at least 20% or 10% between the 2 groups.

In contrast, results were interesting for secondary outcomes in per protocol population analysis, with the limitation of less valuable significance. We considered a 2-point change in the INCAT disability scale to have clinical significance in IgM anti-MAG demyelinating neuropathy. On the other hand, we share the concerns of Dalakas and coworkers as the INCAT disability scale is clearly poor at capturing proprioceptive function and therefore overall improvement. Consequently, we suggest that ISS and INCAT disability scale are not the most appropriate primary outcome measures for assessing paresthesia, pain, and ataxia, which seem to respond better to treatment in these patients. A better scale for primary endpoint in trials for patients with anti-MAG demyelinating neuropathy is therefore needed.

Differences between groups were also found for 2 other clinical secondary outcomes in per protocol analysis. In the previously described trial,¹⁸ the authors reported differences for certain secondary outcomes. Time taken to walk 10 meters was lower in the rituximab group ($p = 0.042$) in the Dalakas et al. study, but no difference occurred in the present study. This was also true for the patients' own assessments, as in our study.

Our results confirmed the median change in B-cell and CD20 cell counts reported in previous studies,^{14,15,18}

but it is unclear whether this reflects the beneficial effect of rituximab in IgM anti-MAG demyelinating neuropathy. It would be important to determine levels of B-cell-activating factor (BAFF), which controls B-cell homeostasis, to further understand the role of these cells in treatment. Serum BAFF concentrations were measured in 23 patients with IgM anti-MAG neuropathy, before and after rituximab therapy, and in 20 neurologic controls and 14 healthy subjects.²⁹ The conclusion was that serum BAFF concentrations could be used to predict the response to treatment. Another report claims that those rituximab-treated patients who show no clinical improvement have a higher load of clonal IgM memory B-cell expansions before and after treatment, a persistence of clonal expansions despite efficient B-cell depletion, and a lack of substantial changes in somatic hypermutation frequencies of IgM memory cells when compared to clinical responders.³⁰

The frequency of adverse events per infusion was low with rituximab and did not differ from placebo, although the total number of withdrawals was higher in the rituximab group (6 of 26) compared to the placebo group (1 of 28; $p = 0.047$). These results are consistent with other rituximab studies.^{14–18} There were 6 serious AE in the rituximab group and 2 in the placebo group ($p = 0.15$), but some were considered unrelated to the treatment. Finally, no obvious consequences of B-cell depletion, no impairment of clinical immunity, and no signs of opportunistic infections were noted.

The present results could be used as the basis for future trials investigating different dose regimens³¹ and combination therapy.³² Further studies are required to determine the best long-term management for patients with IgM anti-MAG demyelinating neuropathy and to identify optimal biomarkers for the response to immunomodulatory therapies.

AUTHOR CONTRIBUTIONS

Jean-Marc Léger: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Karine Viala: drafting/revising the manuscript, study concept or design, acquisition of data. Guillaume Nicolas: drafting/revising the manuscript, acquisition of data. Alain Créange: drafting/revising the manuscript, study concept or design, acquisition of data, study supervision. Jean-Michel Vallat: study concept or design, analysis or interpretation of data, acquisition of data. Jean Pouget: analysis or interpretation of data, acquisition of data. Pierre Clavelou: drafting/revising the manuscript, acquisition of data. Christophe Vial: drafting/revising the manuscript, acquisition of data. Andreas Steck: study concept or design, obtaining funding. Lucile Musset: analysis or interpretation of data. Benoit Marin: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis.

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