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ORIGINAL ARTICLE

Efficacy of rituximab in anti-myelin-associated glycoprotein demyelinating polyneuropathy: Clinical, hematological and neurophysiological correlations during 2 years of follow-up

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Abstract

Background and purpose: We evaluated the clinical and neurophysiological efficacy of rituximab (RTX) in a neurophysiologically homogeneous group of patients with monoclonal gammopathy and immunoglobulin M (IgM) anti-myelin-associated glycoprotein antibody (anti-MAG) demyelinating polyneuropathy.

Methods: Twenty three anti-MAG-positive polyneuropathic patients were prospectively evaluated before and for 2 years after treatment with RTX 375 mg/m^2. The Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale (INCAT-ds), modified INCAT sensory score (mISS), Medical Research Council sum score, Patients' Global Impression of Change scale were used, IgM levels were assessed and extensive electrophysiological examinations were performed before (T0) and 1 year (T1) and 2 years (T2) after RTX treatment.

Results: At T1 and T2 there was a significant reduction from T0 both in mISS and in INCAT-ds, with a p value <0.001 in the inferential Friedman's test overall analysis. Ulnar nerve Terminal Latency Index and distal motor latency significantly changed from T0 to T1 and in the overall analysis ($p = 0.001$ and $p = 0.002$), and ulnar nerve sensory nerve action potential (SNAP) amplitude was significantly increased at T2 from T1, with a p value <0.001 in the overall analysis. Analysis of the receiver-operating characteristic curves showed that a 41.8% increase in SNAP amplitude in the ulnar nerve at T2 from T0 was a fair predictor of a mISS reduction of ≥2 points (area under the curve 0.85; $p = 0.005$; sensitivity: 90.9%, specificity: 83.3%).

Mattia Parisi and Irene Dogliotti are cofirst authors.

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Conclusions: This study suggests that RTX is effective in patients with clinically active demyelinating anti-MAG neuropathy over 2 years of follow-up, and that some neurophysiological variables might be useful for monitoring this efficacy.

KEYWORDS
polyneuropathy, clinical neurophysiology, immunomodulatory therapy, haematological disorders

INTRODUCTION

Monoclonal gammopathy occurs in approximately 1% of the general population, but its prevalence increases with age, being >5% in individuals older than 70 years [1]. In most cases it is a condition with "undetermined significance" (monoclonal gammopathy of undetermined significance [MGUS]), but in some cases monoclonal gammopathy may be related to a hematological disorder. Paraproteinemic demyelinating immunoglobulin M (IgM)-related neuropathy (PDN) is often characterized by a chronic, slowly progressive, predominantly sensory distal symmetric neuropathy with ataxia, often with postural tremor at the upper limbs, with relatively mild or no weakness at the beginning of disease [2–5]. A hallmark of PDN is evidence of anti-myelin-associated glycoprotein IgM antibodies (anti-MAG) in the serum [6], with these being present in approximately half of all patients [7–12].

In electrodiagnostic (EDX) studies, anti-MAG PDN often fulfils the definite electrophysiological criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [10], but frequently shows a "typical anti-MAG" pattern with symmetrical and predominantly distal involvement [3, 10, 13, 14]. PDN patients may be heterogeneous with regards to clinical appearance, anti-MAG level, EDX pattern [15], and response to therapy (poor response to intravenous immunoglobulin or corticosteroids for patients showing a typical anti-MAG pattern on EDX study) [16]. Furthermore, in some patients with PDN and a typical anti-MAG pattern, anti-MAG are undetectable, are detected at very low level or are not pathogenic [6, 17, 18].

This neuropathy may become very disabling, mainly as a result of long disease duration or when axonal damage and motor impairment occur [19], and the response to immunotherapies remains suboptimal. Although many open-label studies indicate that rituximab (RTX), humanized monoclonal antibody against anti-CD20 antigen, is helpful in 30%–50% of patients [20–23], two randomized double-blind, placebo-controlled studies with RTX have failed to reach their clinical primary endpoint [24, 25]. Too low sensitivity of the clinical scales used, a too short follow-up, an inadequate cumulative RTX dose for the most severely affected patients, inclusion of patients with nonprogressive or too long/end-stage disease, neurophysiological inhomogeneity of patients (poor responders among patients with CIDP-like pattern in EDX studies), and severe axonal loss before starting therapy (irreversible nerve damage) may explain the failure of these trials [17, 19, 20, 26–29]. In fact, a recent literature review recommended single-agent RTX as the first option for patients with anti-MAG or anti-ganglioside antibody IgM neuropathy, with ibrutinib being the most promising option in refractory patients [30]. In this context, we aimed to evaluate the long-term clinical and neurophysiological efficacy of RTX in a homogeneous group of IgM-MGUS patients with anti-MAG PDN.

METHODS

Study design

A 2-year longitudinal observational study was carried out by the Neurology and Haematology Divisions of University Hospital "Città della Salute e della Scienza di Torino", Turin, Italy. The study, registered and approved by the Hospital Ethics Committee (number 00205), commenced in October 2017. All patients signed informed consent for the study and for RTX administration as per clinical practice.

Patient selection and treatment

Between October 2017 and December 2020, 59 patients with IgM monoclonal gammopathy (both MGUS and Waldenström macroglobulinemia [WM]) and suspected neuropathy were sequentially evaluated. Exclusion criteria were: diseases known to cause neuropathy (diabetes mellitus, renal or liver disorders, thyroid diseases, alcohol dependence, vitamin deficiency, autoimmune diseases, and drugs); other hematological malignancies; treatment with RTX or other chemotherapy drug in the past 2 years, or with corticosteroids and intravenous immunoglobulin G in the past 6 months; or electromyographic evidence in both lower limbs of polyneuropathic denervation or a recruitment pattern lower than intermediate, indicating significant motor nerve axonal damage. We included patients presenting with ataxia, paresthesia (with or without tremor), IgM monoclonal gammopathy, anti-MAG positivity (>1000 Bühlmann titer units), an Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale (INCAT-ds) score ≥1, a modified INCAT sensory score (mISS) ≥4 with evidence in the last year of clinical or neurophysiological worsening (increase of ≥2 points in mISS, or ≥1 point in INCAT-ds, or 20% reduction of conduction velocity in at least two nerves), and showing on EDX study either a typical anti-MAGpattern, or a CIDP-like pattern associated with a high level of anti-MAG antibodies (>10,000 Bühlmann titer units).

All included patients received four weekly infusions of 375 mg/m^2 RTX.

Neurological and neurophysiological assessment

Neurological and neurophysiological examinations were performed at baseline (T0 [1 month before starting RTX]), and then at 1 year (T1) and 2 years (T2) after RTX treatment. The clinical neurological assessments used were: the Medical Research Council (MRC) sum score, which uses scores of 5 (normal) to 0 for the power assessment of three muscle districts in the upper limbs (wrist and elbow extension, shoulder abduction), and three muscle districts in the lower limbs (foot and knee extension and hip flexion), ranging from 60 (normal) to 0; the INCAT-ds [31], a 10-point scale (5 for upper limbs and 5 for lower limbs), on which 0 represents absence of disability and 5 the complete loss of function; the mISS [32], ranging from 0 (normal sensation) to 33; the seven-point Patients Global Impression of Change (PGIC) scale, ranging from 0 (very much improved) to 7 (very much worse) [33–35].

The neurophysiological study was performed using a Dantec Keypoint machine with an electrical stimulator (interelectrode distance of 2.5 cm and superficial electrodes with diameter of 2 cm). For electroneurographic study, a stimulus with duration of 0.1 ms, and a signal bandwidth 20 Hz–10 kHz were used. Motor and sensory nerve conduction variables were assessed using a standard method, with surface electrodes for stimulation and recording [36], including the following: median nerve, ulnar nerve, peroneal nerve, tibial nerve, and sural nerves. We included F-wave studies, stimulating the ulnar nerves at the wrist and tibial nerves at the ankle. For the ulnar and median nerves, Terminal Latency Index (TLI) score (distance between wrist stimulus site and recording surface)/(motor conduction velocity × distal motor latency [DML]) was calculated: a TLI <0.25 was considered indicative of distal demyelination. [10]. Electromyography with a 0.45-mm diameter coaxial needle electrode was performed at baseline patient evaluation. For the purpose of this study, patients were classified as having a neurophysiological CIDP-like pattern when showing a demyelinating polyneuropathy fulfilling the EFNS/PNS criteria for CIDP [10], or as having a neurophysiological typical anti-MAG pattern when showing a distally predominant demyelination, a greater decrease in sensory nerve action potential (SNAP) amplitudes in the lower than the upper limbs, and no conduction block or temporal dispersion [10].

According to clinical practice, patients received further follow-up every year beyond the 2-year follow-up study, using the same clinical and neurophysiological assessment. Data from the subgroup of patients with follow-up >2 years after RTX treatment were exploratorily analysed.

Hematological evaluation

All patients underwent routine laboratory tests before therapy, and then every 6 months up to 2 years from the start of RTX treatment, or when clinically necessary. IgM level was determined using a nephelometric assay at baseline, and then at 1 year and 2 years after RTX initiation. Baseline paraproteinemia was evaluated by serum and urinary immunofixation electrophoresis. Baseline serum IgM anti-MAG were tested with the Bühlmann GanglioCombi® ELISA method (cut-off 1000 units).

All patients also underwent further hematological investigations, including a bone marrow biopsy and aspirate to confirm overt WM disease or IgM MGUS; flow cytometry analysis on bone marrow aspirate was performed to detect WM B-cell clones and droplet digital PCR was performed to detect MYD88L265P gene mutation on bone marrow aspirate and peripheral blood samples [37].

Statistical analysis

Continuous variables are summarized as mean with standard deviation and median with interquartile range (IQR), as appropriate; categorical data are expressed as frequency and percentage. A last observation carried forward approach for imputing missing data was used. The evaluation of changes over time in each continuous variable (scales and nerve conduction measurements) was performed using Friedman's test, followed by Wilcoxon's signed-rank test for pairwise comparisons (p value adjusted using a false discovery rate approach). The analysis of neurophysiological variables was performed twice, considering both the patients as observation units (and then for each patient calculating the mean value for the right and left sides) and each measurement as a single observation unit. Results refer to two-tailed p values, alpha = 0.05. Receiver-operating characteristic (ROC) curve analysis was graphed for calculation of the area under the curve (AUC) and for identifying the optimal cut-off for ulnar nerve SNAP and compound muscle action potential (CMAP) amplitude percent increase from baseline (%Δ-SNAP and %Δ-CMAP, respectively) for clinical improvement prediction, defined as mISS reduction (by calculating Youden's index). Comparisons between neurophysiologically and hematologically clustered groups were made using the chi-squared test.

Statistical analyses were performed using IBM SPSS Statistics v23.

RESULTS

Patient characteristics

From October 2017, 59 patients with IgM monoclonal gammopathy (37 WM/22 MGUS) and suspected neuropathy were consecutively assessed by clinical and neurophysiological examination at our Neurology Department, and large-fiber polyneuropathy was confirmed in 44 patients. Patient selection was made according to the inclusion criteria, as shown in Figure 1. Thus, we included in the study 23 patients with anti-MAG-positive demyelinating polyneuropathy who showed clinical worsening, defined as an increase of ≥1 point on the INCAT-ds scale or ≥2 points on the mISS scale in the last 1 year. All patients completed the 2-year follow-up evaluations.

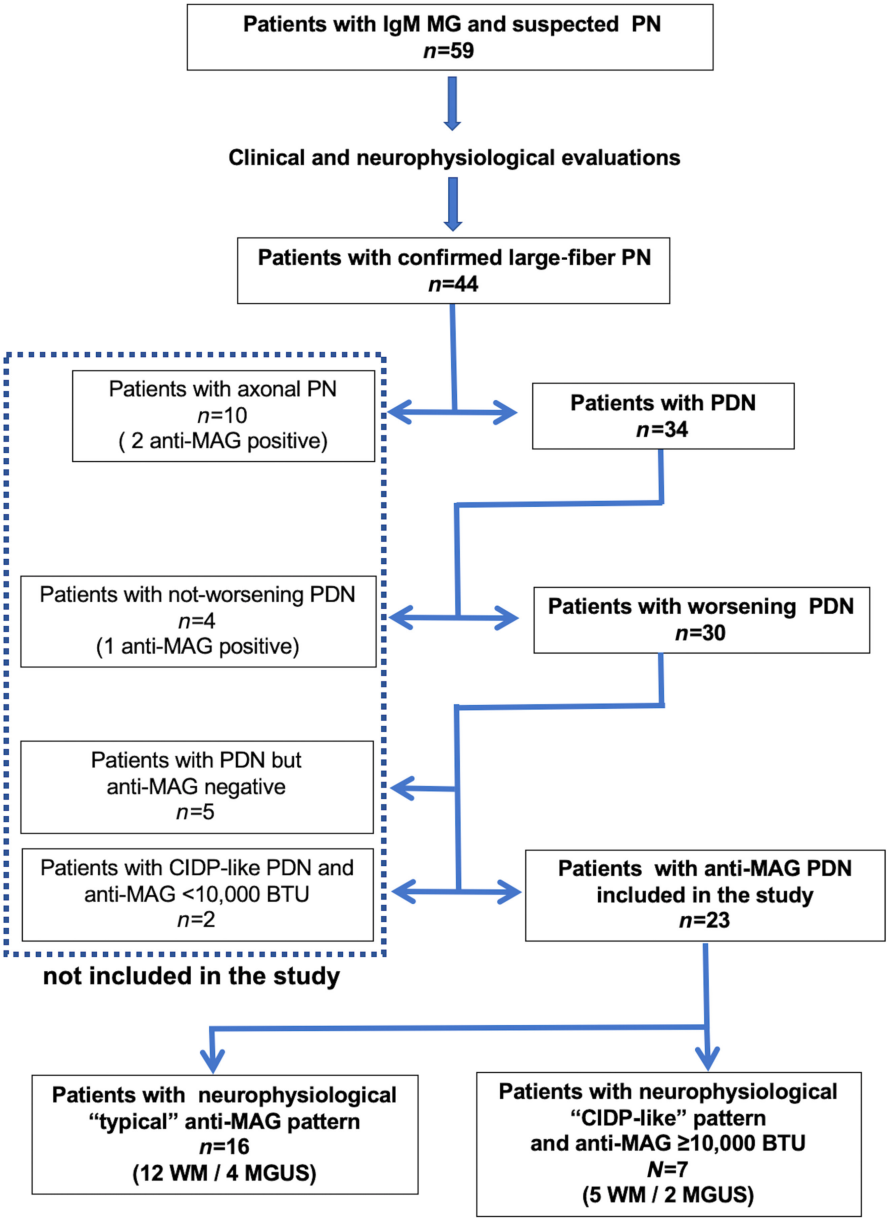

FIGURE 1 Flow chart showing selection of patients included in this study. anti-MAG, anti-myelin-associated glycoprotein antibody; BTU, Bühlmann titer unit; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; IgM MG, immunoglobulin M monoclonal gammopathy; MGUS, monoclonal gammopathy of undetermined significance; PDN, paraproteinemic demyelinating immunoglobulin M-related neuropathy; PN, peripheral neuropathy; WM, Waldenström macroglobulinemia

Table 1 shows the baseline demographic and clinical characteristics of patients included in the analyses. The mean age at baseline was 71.2 ± 8.10 years, 69.6% of patients were male and PDN duration was 4.1 ± 3.1 years. The mean baseline INCAT-ds score and mISS were 2.4 ± 1.3 and 10.9 ± 4.1, respectively.

Immunoglobulin M k-light chain was involved in 20 patients (three patients with IgM λ-chain were in the typical anti-MAG group), and two out of 22 evaluable WM patients had MYD88 wild-type disease.

One patient had received paclitaxel and carboplatin for ovarian cancer 3 years before IgM monoclonal gammopathy diagnosis, and three WM patients had been previously successfully treated with RTX alone (two patients) or RTX and cyclophosphamide (one patient) 3–8 years before inclusion in this study. No WM-related constitutional symptoms, cytopenia, adenopathy or signs of amyloidosis were detected in any patient.

Clinical RTX efficacy

There was a significant improvement in mISS, both at T1 and T2 (overall $p < 0.001$), with scores ranging from 10.9 ± 4.2 at T0, to 10.0 ± 4.4 at T1 and 9.5 ± 5.0 at T2 (Table 2). Seven patients had improvement of ≥2 points and three patients had improvement of

TABLE 1 Baseline demographic, clinical, haematological and neurophysiological characteristics of patients affected by demyelinating polyneuropathy with anti-myelin-associated glycoprotein antibody immunoglobulin M monoclonal gammopathy treated with rituximab

		Neurophysiologically clustered patients			Hematologically clustered patients		
Variable	**Overall**	**Typical anti-MAG pattern**	**CIDP-like pattern**	***p* Value**	**WM**	**MGUS**	***p* value**
Number of patients	23	16	7	ns	17	6	ns
Age, mean ± SD years	71.2 ± 8.1	73.1 ± 6.9	67.0 ± 9.5	ns	70.9 ± 8.6	72.2 ± 6.9	ns
Male/female, *n*	16/7	9/7	7/0	ns	13/4	3/3	ns
Disease duration, years				ns			ns
Mean ± SD	4.1 ± 3.1	4.4 ± 3.5	3.4 ± 2.0		4.3 ± 3.0	3.3 ± 3.6	
Median (IQR)	3.7 (1.8–4.9)	3.9 (1.8 ± 4.8)	3.4 (1.7–4.7)		3.9 (2.0–5.0)	2.6 (1.0–3.8)	
INCAT-ds score				0.006			ns
Mean ± SD	2.4 ± 1.3	2.8 ± 1.3*	1.4 ± 0.8*		2.5 ± 1.5	2.0 ± 0.0	
Median (IQR)	2 (2–3)	2 (2–3.3)	1 (1–1.5)		2 (1–3)	2.0 (2–2)	
mISS				ns			ns
Mean ± SD	10.9 ± 4.2	11.7 ± 4.3	9.0 ± 3.3		11.4 ± 4.4	9.5 ± 3.4	
Median (IQR)	10 (7.5–13.5)	11 (7.7–14.5)	9 (7–10)		11 (8–14)	8.5 (7.3–9.8)	
MRC score				ns			ns
Mean ± SD	57.9 ± 2.1	57.7 ± 2.1	58.4 ± 2.3		57.8 ± 2.4	58.2 ± 1.2	
Median (IQR)	58 (58–60)	58 (58–59)	60 (57.5–60)		58 (58–60)	57 (58–59.5)	
Ataxia/Tremor, *n*	23/8	16/7	7/1	ns	17/6	6/1	ns
IgM level, g/L				ns			ns
Mean ± SD	6.6 ± 3.9	7.2 ± 3.9	5.4 ± 3.8		6.3 ± 3.5	7.6 ± 5.0	
Median (IQR)	6.2 (3.3–10.4)	6.2 (3.4–10.7)	3.8 (3.0–7.4)		6.2 (3.4–8.3)	7.6 (3.5–11.7)	
Anti-MAG, BTU				ns			ns
Mean ± SD	61,444 ± 49,569	67,090 ± 51,750	52,571 ± 48,455		67,500 ± 56,629	49,333 ± 32,173	
Median (IQR)	52,500 (28,500-70,000)	70,000 (40,000-70,000)	50,000 (21,500-60,000)		60,000 (41250-70,000)	42,500 (28,500-66,250)	
WM/MGUS, *n*	17/6	12/4	5/2	ns	-	-	
MYD88 positive, *n*	20 on 22 assayed	15	5		14	6	
Neurophysiology							
CIDP-like, *n*	7	-	-		5	2	
Typical anti-MAG, *n*	16	-	-		12	4	

Note: "CIDP-like" and "Typical anti-MAG" are defined according to neurophysiological criteria of CIDP and IgM paraproteinemic demyelinating neuropathy (Joint Task Force of the EFNS and the PNS, 2010).

Abbreviations: anti-MAG, immunoglobulin M anti-myelin-associated glycoprotein antibody; BTU, Bühlmann titer unit; CIDP, chronic inflammatory demyelinating polyneuropathy; IgM, immunoglobulin M; INCAT-ds, Inflammatory Neuropathy Cause and Treatment Disability Scale; IQR, first to third interquartile range; MGUS, monoclonal gammopathy of undetermined significance; mISS, modified inflammatory neuropathy cause and treatment sensory score; MRC, Medical Research Council; MYD88 positive, presence of L265P mutation at MYD88 gene; *n*, number of patients; ns, nonsignificant; SD, standard deviation; WM, Waldenström macroglobulinemia.

*Significantly different ($p < 0.05$) each other.

TABLE 2 Results for the analysis of clinical scores and haematological variables during 2-year follow-up of 23 patients affected by demyelinating polyneuropathy with anti-myelin-associated glycoprotein antibody immunoglobulin M monoclonal gammopathy treated with rituximab

				p value	
Variable	**Baseline (T0)**	**1-year (T1)**	**2-years (T2)**	**Overall**	**Comparisons**
mISS					
Mean ± SD	10.9 ± 4.2	10.0 ± 4.4	9.5 ± 5.0	<0.001	T0 vs. T1: 0.030
Median (IQR)	10.0 (7.5–13.5)	10.0 (7.0–13)	8 (6–12.5)		T1 vs. T2: 0.16
					T0 vs. T2: 0.006
INCAT-ds score					
Mean ± SD	2.4 ± 1.3	1.9 ± 1.3	1.9 ± 1.4	<0.001	T0 vs. T1: 0.013
Median (IQR)	2.0 (2.0–3.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)		T1 vs. T2: 0.59
					T0 vs. T2: 0.006
INCAT-ds score, upper limbs					
Mean ± SD	1.0 ± 0.9	0.7 ± 0.8	0.7 ± 0.8	0.003	T0 vs. T1:0.036
Median (IQR)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.0 (0.0–1.0)		T1 vs. T2: 0.71
					T0 vs. T2: 0.024
INCAT-ds score, lower limbs					
Mean ± SD	1.4 ± 0.7	1.3 ± 0.8	1.2 ± 0.8	0.030	T0 vs. T1: 0.090
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–1.5)	1.0 (1.0–1.5)		T1 vs. T2: 0.56
					T0 vs. T2: 0.10
MRC sum score					
Mean ± SD	58.0 ± 2.2	58.4 ± 2.0	58.5 ± 2.0	0.010	
Median (IQR)	58.0 (58.0–60.0)	59.0 (58.0–60.0)	59.0 (58.0–60.0)		
PGIC scale					
Mean ± SD		3.4 ± 1.2	3.2 ± 1.3	0.325	
Median (IQR)		4.0 (2.0–4.0)	4.0 (2.0–4.0)		
IgM level, g/l					
Mean ± SD	6.6 ± 3.9	4.3 ± 2.8	4.4 ± 3.5	<0.001	T0 vs. T1: <0.001
Median (IQR)	6.2 (3.3–10.4)	3.6 (2.0–6.1)	3.3 (1.9–5.1)		T1 vs. T2: 0.236
					T0 vs. T2: <0.001

Abbreviations: IQR, first to third interquartile range; IgM, immunoglobulin M; INCAT-ds, Inflammatory Neuropathy Cause and Treatment Disability Scale; mISS, modified Inflammatory Neuropathy Cause and Treatment Sensory Score; MRC, Medical Research Council; PGIC, seven-point-Patients Global Impression of Change.

≥4 points at T1, and in 11 patients mISS improved by ≥2 points and in three patients by ≥4 points at T2. One patient had a worse mISS at T1 and mISS was equal to its baseline value at T2. INCAT-ds showed significant improvement both at T1 and T2 (overall $p < 0.001$), with scores ranging from 2.4 ± 1.3 at T0, to 1.9 ± 1.3 at T1 and 1.9 ± 1.4 at T2. Three patients improved by ≥2 points at T1, and two patients at T2 when compared with baseline. No patients showed a worsening during follow-up. MRC sum score and the PGIC scale showed no significant change during follow up ($p = 0.325$).

Serum IgM level significantly decreased both at T1 and T2 evaluation ($p < 0.001$). There were no hematological complications during 2-year follow-up. Only one patient showed hematological disease progression, requiring therapy with ibrutinib 6 months after the end of the study. As expected, RTX had a highly manageable safety profile, with only nine Grade 2 infusion-related reactions. No serious adverse events or infections were reported during and after RTX treatment.

Neurophysiological features

Neurophysiological characteristics are summarized in Table 3 (upper limbs) and Table 4 (lower limbs). At the 2-year evaluation, there were significant variations in TLI, DML, CMAP and SNAP amplitudes in the ulnar nerve, both with regard to total number of measurements ($p < 0.05$) and left–right mean ($p = 0.011$, $p = 0.019$), with values trending toward significance for TLI and DML ($p = 0.07$).

The post hoc analysis showed significant change in ulnar nerve TLI and DML in the first year of follow-up, and in ulnar and median nerve CMAP and ulnar, median and sural nerve SNAP amplitudes in the second year of follow-up. Median and ulnar CMAP negative peak duration was reduced significantly in the first year of follow-up.

No significant changes occurred in other measured variables.

The ROC curve analysis showed that the percentage increase in ulnar nerve SNAP amplitude at T2 from T0 (%Δ-SNAP; Figure 2) was a fair predictor of the clinical change: the AUC was 0.85 (95% CI

TABLE 3 Results for the analysis of neurophysiological characteristics of the upper limbs during 2-year follow-up of 23 patients affected by demyelinating polyneuropathy with anti-myelin-associated glycoprotein antibody immunoglobulin M monoclonal gammopathy treated with rituximab

				p value			
	Baseline (T0)	1-year (T1)	2-years (T2)	Overall		Statistically significant comparisons	
Variable	mean ± SD	mean ± SD	mean ± SD	Left–right mean	Total number of measurements	Left–right mean	Total number of measurements
Ulnar nerve							
DML, ms	5.1 ± 2.0	4.6 ± 2.0	4.8 ± 2.3	0.07	**0.002**	T0 vs. T1: 0.05 T1 vs. T2: 0.794 T0 vs. T2: 0.108	T0 vs. T1: **0.004** T1 vs. T2: 0.08 T0 vs. T2: **0.006**
TLI	0.36 ± 0.10	0.42 ± 0.10	0.38 ± 0.10	0.07	**0.001**	T0 vs. T1:**0.015** T1 vs. T2: **0.039** T0 vs. T2: 0.394	T0 vs. T1: <**0.001** T1 vs. T2: **0.043** T0 vs. T2: 0.57
CMAP amplitude, mV	5.2 ± 2.3	5.5 ± 2.1	6.1 ± 2.5	**0.011**	**0.001**	T0 vs. T1: 0.27 T1 vs. T2: 0.07 T0 vs. T2: **0.015**	T0 vs. T1: 0.083 T1 vs. T2: **0.030** T0 vs. T2: <**0.001**
MCV, m/s	37.1 ± 12.1	37.2 ± 11.3	36.8 ± 11.9	0.503	0.758	T0 vs. T1: 0.455 T1 vs. T2: 0.835 T0 vs. T2: 0.903	T0 vs. T1: 0.265 T1 vs. T2: 0.856 T0 vs. T2: 0.645
Negative peak duration of distal CMAP, ms	7.8 ± 1.5	7.1 ± 1.3	7.3 ± 1.4	0.156	0.229	T0 vs. T1: **0.01** T1 vs. T2: 0.273 T0 vs. T2: 0.106	T0 vs. T1: **0.004** T1 vs. T2: 0.206 T0 vs. T2: 0.067
SNAP amplitude, μV	3.1 ± 4.2	3.7 ± 4.2	5.9 ± 6.0	**0.019**	**0.001**	T0 vs. T1: 0.3 T1 vs. T2: **0.015** T0 vs. T2: **0.027**	T0 vs. T1: 0.25 T1 vs. T2: <**0.001** T0 vs. T2: **0.003**
SCV, m/s	34.5 ± 12.6	36.3 ± 9.0	35.2 ± 9.5	0.097	0.227	T0 vs. T1: 0.152 T1 vs. T2: 0.463 T0 vs. T2: 0.311	T0 vs. T1: 0.153 T1 vs. T2: 0.2 T0 vs. T2: 0.315
F wave latency, ms	49.3 ± 20.0	46.8 ± 18.9	44.3 ± 13.3	0.988	0.819	T0 vs. T1: 0.877 T1 vs. T2: 0.460 T0 vs. T2: 0.823	T0 vs. T1: 0.858 T1 vs. T2: 0.746 T0 vs. T2: 0.823
Median nerve							
DML, ms	8.6 ± 4.1	8.6 ± 5.3	8.3 ± 5.2	0.190	0.636	T0 vs. T1: 0.412 T1 vs. T2: 0.733 T0 vs. T2: **0.039**	T0 vs. T1: 0.604 T1 vs. T2: 0.365 T0 vs. T2: 0.239
TLI	0.26 ± 014	0.22 ± 0.06	0.22 ± 0.07	0.529	0.584	T0 vs. T1: 0.394 T1 vs. T2: 0.859 T0 vs. T2: 0.221	T0 vs. T1: 0.566 T1 vs. T2: 0.936 T0 vs. T2: 0.948
CMAP amplitude, mV	4.5 ± 2.7	4.5 ± 2.6	5.1 ± 3.2	0.131	0.355	T0 vs. T1: 0.972 T1 vs. T2: 0.151 T0 vs. T2: **0.012**	T0 vs. T1: 0.952 T1 vs. T2: 0.113 T0 vs. T2: **0.02**
MCV, m/s	32.7 ± 11.1	34.7 ± 10.9	37.0 ± 10.0	0.584	0.696	T0 vs. T1: 0.503 T1 vs. T2: 0.592 T0 vs. T2: 0.855	T0 vs. T1: 0.088 T1 vs. T2: 0.635 T0 vs. T2: 0.220
Negative peak duration of distal CMAP, ms	7.9 ± 2.5	7.0 ± 1.6	6.7 ± 1.4	0.065	**0.018**	**T0 vs. T1: 0.012** T1 vs. T2: 0.627 T0 vs. T2: 0.097	**T0 vs. T1: 0.003** T1 vs. T2: 0.4 **T0 vs. T2: 0.037**
SNAP amplitude, μV	2.4 ± 3.7	3.2 ± 3.9	4.0 ± 5.0	**0.037**	0.163	T0 vs. T1: 0.133 T1 vs. T2: 0.187 **T0 vs. T2: 0.039**	T0 vs. T1: 0.107 T1 vs. T2: 0.082 **T0 vs. T2: 0.017**

(Continues)

TABLE 3 (Continued)

				p value			
	Baseline (T0)	1-year (T1)	2-years (T2)	Overall		Statistically significant comparisons	
Variable	mean ± SD	mean ± SD	mean ± SD	Left–right mean	Total number of measurements	Left–right mean	Total number of measurements
SCV, m/s	42.0 ± 11.1	38.8 ± 12.0	37.9 ± 9.8	0.695	0.441	T0 vs. T1: 0.583 T1 vs. T2: 0.433 T0 vs. T2: 0.790	T0 vs. T1: 0.972 T1 vs. T2: 0.102 T0 vs. T2: 0.388

Note: Bold was used to show values statistically significant $p < 0.05$. For neurophysiological variables comparisons were made using the side-to-side mean ("left–right mean") and considering each nerve as a single unit ("total number of measurements").

Abbreviations: CMAP, compound muscle action potential; DML, distal motor latency; MCV, motor conduction velocity; ns, no significance; SCV, sensory conduction velocity; SNAP, sensory nerve action potential; TLI, Terminal Latency Index.

0.67–1.00; $p = 0.005$), suggesting that a cut-off set at 41.8% of SNAP increase can discriminate patients with mISS reduction of ≥2 points at T2 from baseline (sensitivity: 90.9%, specificity: 83.3%).

Except for the INCAT-ds score scale, which was significantly higher in patients with the typical anti-MAG phenotype, no differences were found at baseline (Table 1) and we mean that we did not find differences at baseline and in the response to the therapy (using clinical scales values, laboratory value and neurophysiological characteristics) comparing the subgroups (hematologically MGUS vs. WM and neurophysiologically typical vs. CIDP).

Thirteen patients reached a follow-up >2 years, and these results showed a tendency towards progressive loss of efficacy of the therapy; after 3.5 years follow-up, four patients required new treatment, with three patients being re-treated with RTX for neurological deterioration, and one patient being treated with ibrutinib for hematological progression.

DISCUSSION

Several previous studies have shown that patients with PDN associated with anti-MAG are not a homogenous group [17–19]. The differing clinical, antibody and neurophysiological characteristics of these patients are probable reasons for the variability in response to therapies and explain the discordant results of RTX reported for this disease.

Our study demonstrated the clinical and neurophysiological response to RTX, maintained for at least 2 years in patients were selected on the basis of neurological, neurophysiological and haematological elements. The multidisciplinary approach is based on awareness of both the heterogeneity of the disease and the lack of standard care, which often hinder therapeutic options, especially when criteria for malignant processes are not met [38]. In this study, patient selection was based on the neurophysiological hallmark of the disease, the distal demyelination, and the level of anti-MAG antibodies. We deliberately addressed to the therapy and included in the study patients with a typical clinical presentation but with an atypical neurophysiological phenotype (CIDP-like) when they presented high levels of anti-MAG antibodies. We underline that, in such patients, the treatment decision should be based on the anti-MAG antibody titer. Highly elevated levels of anti-MAG antibodies are more likely to be diagnostic (and pathogenic) than mildly elevated titers [39]. We believe that this is important because of implications for treatment indication and subsequent possible benefit.

Our population had a lower mean disease duration in comparison to some previous studies [17, 25, 27], and no significant motor nerve axonal damage, suggesting that nerve damage was not yet too severe and therefore potentially reversible after therapy [19, 20, 26–29].

Clinical efficacy of RTX therapy

We chose to use the INCAT-ds score as the disability scale because this has been validated for the evaluation of various inflammatory demyelinating neuropathies, including IgM anti-MAG neuropathy [25, 40, 41]. We chose the mISS because it takes into account a greater number of sensory variables than the INCAT sensory score by adding light touch and joint position evaluation, thus increasing the sensitivity for detecting clinical changes [32, 42]. As suggested by other studies [24, 25], a change of ≥1 point on the INCAT-ds scale or ≥2 points on the mISS scale can be used as a sensitive measure in identifying improvement or worsening in the individual patient.

The statistically significant decrease in mean mISS and INCAT-ds score in the overall analysis, with a more prominent reduction by the second year from baseline is compatible with a clinical effect starting in the first year after RTX, and persisting and maybe increasing in the second year of follow-up [17]. Notably, our results confirm those reported by Dalakas (excluding the patient who had a normal INCAT score at entry, and thus could not improve) [24].

The upper limbs showed a better response to RTX treatment than the lower limbs in terms of disability, probably because they were less severely affected before starting therapy. The extent and duration of the effectiveness of RTX is not the same for all patients, probably depending on a greater refractoriness to therapy by some lymphocyte clones.

TABLE 4 Results for the analysis of neurophysiological characteristics of the lower limbs during 2-year follow-up of 23 patients affected by demyelinating polyneuropathy with anti-myelin-associated glycoprotein antibody immunoglobulin M monoclonal gammopathy treated with rituximab

				p value			
	Baseline (T0)	1-year (T1)	2-years(T2)	Overall		Statistically significant comparisons	
Variable	mean ± SD	mean ± SD	mean ± SD	Left–right mean	Total number of measurements	Left–right mean	Total number of measurements
Tibial nerve							
DML, ms	9.3 ± 3.3	9.6 ± 4.3	10.8 ± 4.4	0.581	0.403	T0 vs. T1: 0.463 T1 vs. T2: 0.683 T0 vs. T2: 0.427	T0 vs. T1: 0.922 T1 vs. T2: 0.284 T0 vs. T2: 0.224
CMAP amplitude, mV	0.7 ± 1.4	0.7 ± 1.1	0.7 ± 1.0	0.143	0.485	T0 vs. T1: 0.421 T1 vs. T2: 0.660 T0 vs. T2: 0.256	T0 vs. T1: 0.363 T1 vs. T2: 0.577 T0 vs. T2: 0.273
MCV, m/s	31.4 ± 7.9	29.5 ± 10.1	26.8 ± 8.8	0.882	0.913	T0 vs. T1: 0.953 T1 vs. T2: 0.328 T0 vs. T2: 0.779	T0 vs. T1: 0.848 T1 vs. T2: 0.795 T0 vs. T2: 0.709
Negative peak duration of distal CMAP, ms	7.3 ± 3.1	6.9 ± 3.5	7.4 ± 2.8	0.565	0.055	T0 vs. T1: 0.674 T1 vs. T2: 0.203 T0 vs. T2: 0.310	T0 vs. T1: 0.877 T1 vs. T2: 0.300 T0 vs. T2: 0.052
F wave latency, ms	78.5 ± 20.1	81.1 ± 9.1	76.1 ± 5.9	0.331	0.220	T0 vs. T1: 0.499 T1 vs. T2: 0.310 T0 vs. T2: 0.917	T0 vs. T1: 0.398 T1 vs. T2: 0.116 T0 vs. T2: 0.397
Peroneal nerve							
DML, ms	9.8 ± 4.3	9.2 ± 3.8	8.8 ± 3.8	0.368	0.074	T0 vs. T1: 0.250 T1 vs. T2: 0.499 T0 vs. T2: 0.309	T0 vs. T1: 0.139 T1 vs. T2: 0.674 T0 vs. T2: 0.484
CMAP amplitude, mV	0.8 ± 1.2	0.8 ± 1.1	0.7 ± 1.1	1.000	0.651	T0 vs. T1: 0.807 T1 vs. T2: 0.722 T0 vs. T2: 0.530	T0 vs. T1: 0.717 T1 vs. T2: 0.965 T0 vs. T2: 0.717
MCV, m/s	25.9 ± 11.0	26.5 ± 7.3	27.9 ± 7.5	0.869	0.941	T0 vs. T1: 0.917 T1 vs. T2: 0.844 T0 vs. T2: 0.583	T0 vs. T1: 0.763 T1 vs. T2: 0.872 T0 vs. T2: 0.758
Negative peak duration of distal CMAP, ms	6.4 ± 3.2	6.8 ± 1.6	6.0 ± 2.2	0.524	0.408	T0 vs. T1: 0.844 T1 vs. T2: 0.327 T0 vs. T2: 0.350	T0 vs. T1: 0.231 T1 vs. T2: 0.098 T0 vs. T2: 0.293
Sural nerve							
SNAP amplitude, μV	1.7 ± 2.4	1.8 ± 2.7	2.3 ± 3.2	0.449	0.097	T0 vs. T1: 0.917 T1 vs. T2: 0.223 T0 vs. T2: 0.123	T0 vs. T1: 0.937 T1 vs. T2: 0.173 **T0 vs. T2: 0.049**
SCV, m/s	33.3 ± 6.7	37.5 ± 5.2	32.4 ± 8.1	0.449	0.122	T0 vs. T1: 0.249 T1 vs. T2: 0.345 T0 vs. T2: 0.917	T0 vs. T1: 0.084 T1 vs. T2: 0.139 T0 vs. T2: 0.906

Note: Bold was used to show values statistically significant $p < 0.05$. For neurophysiological variables comparisons were made using the side-to-side mean ("left–right mean") and considering each nerve as a single unit ("total number of measurements").

Abbreviations: CMAP, compound muscle action potential; DML, distal motor latency; MCV, motor conduction velocity; ns, no significance; SCV, sensory conduction velocity; SNAP, sensory nerve action potential.

On average, the MRC sum score was only mildly reduced at baseline and did not change significantly over time. These results are in line with the typically sensory-prevailing and motor-sparing nature of anti-MAG neuropathy, with the disability being related to sensory rather than motor deficit.

There were no statistically significant changes in PGIC score in the overall analysis; this finding, shows that the PGIC scale was not very sensitive in this specific case. We did not use a quality-of-life scale for the assessment, and this might be considered a limitation of the study. However, quality of life seems to be poorly correlated

with sensory scales and better related to disability scales, with previous RCTs and a Cochrane review choosing a disability score for their purposes [43].

The clinical efficacy of RTX shown in our study compared to other trials may be linked to the characteristics of the treated patients; patients in our study were homogeneous with regard to electromyographic characteristics ("typical anti-MAG" pattern; "CIDP-like" pattern but with high anti-MAG antibody levels, with exclusion of patients with severe axonal damage), had a short disease duration (mean ± SD 4.1 ± 3.1 years; median 3.7 [IQR1.8–4.9] years), which was significantly shorter than that of patients who received RTX in the study by Dalakas (mean ± SD 12.9 ± 7.2 years), and had lower INCAT-ds scores (median 2 [IQR 2–3]) compared to those described by Leger (median 3 [IQR 2–4]), with INCAT-ds score in the lower extremities (1.4 ± 0.7) similar to that reported in the study by Dalakas (1.45 ± 0.7).

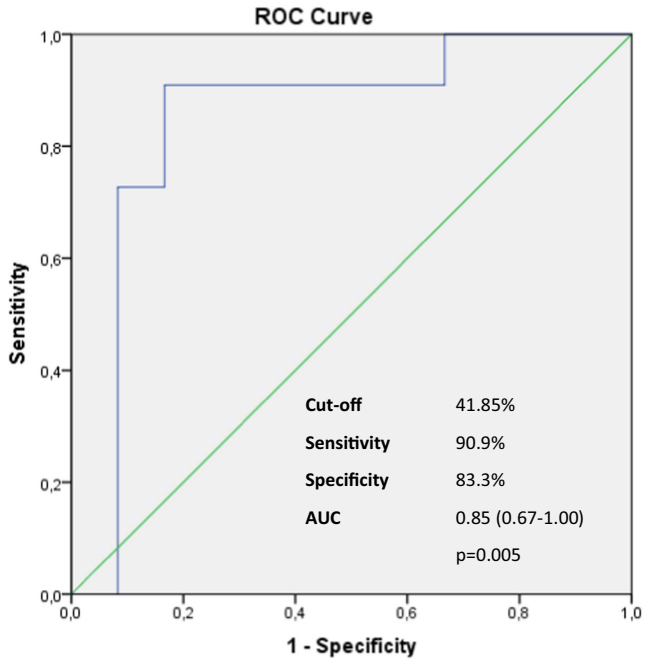

FIGURE 2 Receiver-operating characteristic (ROC) curve analysis of ulnar nerve sensory nerve action potential (SNAP) amplitude percent increase at 2 years compared with baseline value (%Δ-SNAP) for prediction of modified inflammatory neuropathy cause and treatment sensory score (mISS) reduction ≥2 points at 2 years from baseline evaluation. AUC, area under the curve

Hematological efficacy of RTX therapy

Immunoglobulin M level was significantly reduced at 1 year and then stable after 2 years of follow-up, as expected after treatment with an anti-CD20 agent [21]. No patient deteriorated hematologically in the 2 years of follow-up after RTX.

Anti-MAG antibody level was not monitored in the follow-up of our study because of conflicting data on the correlation between autoantibody variation and clinical response to RTX, although one study has shown that a reduction of more than 50% in these antibodies may correlate with clinical improvement after therapy [29]. Frequency and severity of collaterality due to RTX treatment were very low, probably due to premedication given before the drug infusion and the relatively low IgM burden of the patients enrolled (indeed, no patient required plasmapheresis before RTX treatment to avoid flares), and these results are consistent with other RTX studies [20, 21, 24, 25].

Neurophysiological consideration of efficacy of RTX therapy

The main neurophysiological data emerging from our study highlight an asynchronous improvement in some ulnar nerve parameters after RTX therapy: increases in TLI and DML and a decrease in negative peak duration of distal CMAP at 1 year, with subsequent return to baseline at 2 years, and an increase in CMAP amplitude and even greater increase in SNAP amplitude between the first and second year after therapy (Figure 3). These data are even more significant when considering the right and left values independently. Median nerve CMAP and SNAP amplitudes and sural nerve SNAP amplitude also showed significant increases at 2 years from baseline,

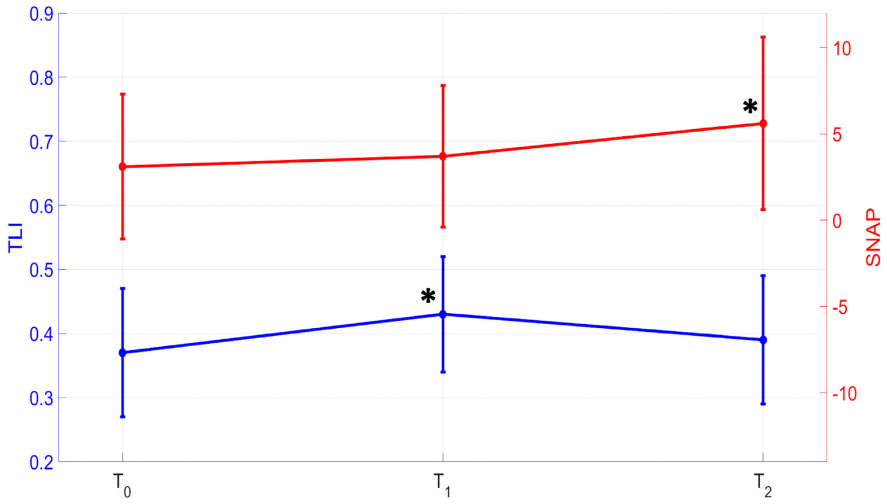

FIGURE 3 Ulnar nerve Terminal Latency Index (TLI) and sensory nerve action potential (SNAP) amplitude variation (mean ± SD) during 2-year follow-up of 23 patients affected by demyelinating polyneuropathy with anti-myelin-associated glycoprotein antibody immunoglobulin M monoclonal gammopathy treated with rituximab

but to a lesser degree than in the ulnar nerve, possibly due to concomitant carpal tunnel syndrome (median nerve) and greater length-dependent axonal damage (sural nerve), which can partially mask the effectiveness of RTX treatment in these nerves.

The neurophysiological data from our study are intriguing because they can explain how RTX exerts its action in anti-MAG PDN. In fact, the increase in TLI and the reduction of negative peak duration of distal CMAP are compatible with an earlier effect of the therapy in reducing the level and therefore the pathogenicity of autoantibodies antibodies directed against components of the myelin sheath, with a consequent reduction of demyelination and chrono-dispersion of the distal tracts of the nerve. On the other hand, the remyelination of the distal tracts of the nerves, a process later than the removal of the pathogenetic cause of demyelination, and the contextual reduction of secondary axonal degeneration, could cause an increase in CMAP and SNAP amplitudes.

Although Bourque et al. recently reported a marked trend towards lower limb motor and sensory potentials becoming unrecordable [44], we did not observe any worsening, but stabilization of these values. The change in SNAP amplitude in the sural nerve, even if only partially significant, seem to be in line with other findings. The early reduction in SNAP amplitude could be considered a "red flag" for the prompt initiation of RTX treatment [45] and we suggest that, in patients with less damage and with shorter disease duration, a partial recovery of SNAP amplitude could be observed.

Based on the ROC curve analysis, we consider that serial monitoring of ulnar nerve SNAP may be used as a paraclinical variable in assessing response to RTX treatment and possibly also other therapies in patients affected by anti-MAG PDN. Furthermore, the correlation found between increase in SNAP amplitude in the ulnar nerve and reduction of even only 2 points in mISS supports the hypothesis that even small variations on this scale (and probably also on other scales currently used in the evaluation of patients with chronic dysimmune polyneuropathy) may already be considered significant in monitoring the efficacy of a therapy. This is in line with a recent meta-analysis [46], which showed that both improvement and stabilization of INCAT overall disability score (INCAT-ODSS) can be considered as favorable outcomes of a therapy carried out in patients with CIDP.

In our experience, after the first year of therapy, neurophysiological monitoring could be useful for the selection of patients who could benefit from retreatment: sometimes the neurophysiological worsening could anticipate clinical worsening. In these cases, we suggest that a stricter follow-up is needed for the final decision. We hope future controlled studies can confirm the validity of this approach and of the use of these parameters in clinical trials.

Conclusions

Neurophysiology can play an important role in the screening of patients with anti-MAG PDN: we provide evidence of objective improvements in neurophysiological characteristics associated with the biological effect of RTX. Ulnar nerve TLI, DML and SNAP amplitude (especially that of the ulnar nerve) showed the potential to be used as paraclinical measures of earlier (TLI) and a later (SNAP amplitude) response to therapy, and for monitoring of changes possibly missed by the current scales which lack sensitivity for clinical changes in these patients.

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CONFLICT OF INTEREST

The authors declare no conflicts of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2002;346(8):564–9.
2. Yeung KB, Thomas PK, King RH, et al. The clinical spectrum of peripheral neuropathies associated with benign monoclonal IgM, IgG and IgA paraproteinaemia. Comparative clinical, immunological and nerve biopsy findings. *J Neurol*. 1991;238(7):383-391.
3. Capasso M, Torrieri F, Di Muzio A, De Angelis MV, Lugaresi A, Uncini A. Can electrophysiology differentiate polyneuropathy with anti-MAG/SGPG antibodies from chronic inflammatory demyelinating polyneuropathy? *Clin Neurophysiol*. 2002;113(3):346-353.
4. Magy L, Chassande B, Maisonobe T, Bouche P, Vallat JM, Léger JM. Polyneuropathy associated with IgG/IgA monoclonal gammopathy: a clinical and electrophysiological study of 15 cases. *Eur J Neurol*. 2003;10(6):677-685.
5. Briani C, Ferrari S, Campagnolo M, et al. Mechanisms of nerve damage in neuropathies associated with hematological diseases: lesson from nerve biopsies. *Brain Sciences*. 2021;11(2):132.
6. Svahn J, Petiot P, Antoine JC, et al. Anti-MAG antibodies in 202 patients: clinicopathological and therapeutic features. *J Neurol Neurosurg Psychiatry*. 2018;89:499-505.
7. Latov N, Braun PE, Gross RB, Sherman WH, Penn AS, Chess L. Plasma cell dyscrasia and peripheral neuropathy: identification of the myelin antigens that react with human paraproteins. *Proc Natl Acad Sci U S A*. 1981;78(11):7139-7142.
8. Kelly JJ Jr. Peripheral neuropathies associated with monoclonal proteins: A clinical review. *Muscle Nerve*. 1985;8(2):138-150.
9. Nobile-Orazio E, Manfredini E, Carpo M, et al. Frequency and clinical correlates of anti-neural IgM antibodies in neuropathy associated with IgM monoclonal gammopathy. *Ann Neurol*. 1994;36(3):416-424.
10. Guideline PNSPDN. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task

Force of the European Federation of Neurological Societies and Peripheral Nerve Society. *J Peripher Nerv Syst*. 2010;195:185-195.
11. Ritz MF, Erne B, Ferracin F, Vital A, Vital C, Steck AJ. Anti-MAG IgM penetration into myelinated fibers correlates with the extent of myelin widening. *Muscle Nerve*. 1999;22(8):1030-1037.
12. Talamo G, Mir MA, Pandey MK, Sivik JK, Raheja D. IgM MGUS associated with anti-MAG neuropathy: a single institution experience. *Ann Hematol*. 2015;94(6):1011-1016.
13. Kaku DA, England JD, Sumner AJ. Distal accentuation of conduction slowing in polyneuropathy associated with antibodies to myelin-associated glycoprotein and sulphated glucuronyl paraglo-boside. *Brain*. 1994;117(5):941-947.
14. Katz JS, Saperstein DS, Gronseth G, Amato AA, Barohn RJ. Distal acquired demyelinating symmetric neuropathy. *Neurology*. 2000;54(3):615.
15. Magy L, Kaboré R, Mathis S, Lebeau P, Ghorab K, Caudie C, Vallat JM Heterogeneity of polyneuropathy associated with anti-mag antibodies. *J Immunol Res* 2015;2015:450391, 1, 9.
16. Dalakas MC, Quarles RH, Farrer RG, et al. A controlled study of intravenous immunoglobulin in demyelinating neuropathy with IgM gammopathy. *Ann Neurol*. 1996;40(5):792-795.
17. Dalakas MC. Advances in the diagnosis, immunopathogenesis and therapies of neuropathies. *Ther Adv Neurol Disord*. 2018;11:1-12.
18. Matà S, Torricelli S, Barilaro A, et al. Polyneuropathy and monoclonal gammopathy of undetermined significance (MGUS); update of a clinical experience. *J Neurol Sci*. 2021;423:117335.
19. Kawagashira Y, Koike H, Ohyama K, et al. Axonal loss in fl uences the response to rituximab treatment in neuropathy associated with IgM monoclonal gammopathy with anti-myelin-associated glycoprotein antibody. *J Neurol Sci*. 2015;348(1–2):67-73.
20. Benedetti L, Briani C, Franciotta D, et al. Long-term effect of rituximab in anti-MAG polyneuropathy. *Neurology*. 2008;71(21):1742-1744.
21. Pestronk A, Florence J, Miller T, Choksi R, Levine TD. Treatment of IgM antibody associated polyneuropathies using rituximab. *Neurol Neurosurg Psychiatry*. 2003;74:485-489.
22. Renaud S, Fuhr P, Gregor M, et al. High-dose rituximab and anti-MAG-associated polyneuropathy. *Neurology*. 2006;66(5):742-744.
23. Niermeijer JMF, Eurelings M, Lokhorst HL, et al. Rituximab for polyneuropathy with IgM monoclonal gammopathy. *J Neurol Neurosurg Psychiatry*. 2009;80(9):1036-1039.
24. Dalakas MC, Rakocevic G, Salajegheh M, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. *Ann Neurol*. 2009;65(3):286-293.
25. Leger JM, Viala K, Nicolas G, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. *Neurology*. 2013;80(24):2217-2225.
26. Pruppers MHJ, Merkies ISJ, Notermans NC. Recent advances in outcome measures in IgM-anti-MAG+ neuropathies. *Curr Opin Neurol*. 2015;28(5):486-493.
27. Gazzola S, Delmont E, Franques J, et al. Predictive factors of efficacy of rituximab in patients with anti-MAG neuropathy. *J Neurol Sci*. 2017;377:144-148.
28. Rakocevic G, Martinez-Outschoorn U, Dalakas MC. Obinutuzumab, a potent anti–B-cell agent, for rituximab-unresponsive IgM anti-MAG neuropathy. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(4):e460.
29. Hänggi P, Aliu B, Martin K, Herrendorff R, Steck AJ. Decrease in serum anti-MAG autoantibodies is associated with therapy response in patients with anti-MAG neuropathy: retrospective study. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(1):e1109.
30. Moreno DF, Rosiñol L, Cibeira MT, Bladé J, Fernández de Larrea C. Treatment of patients with monoclonal gammopathy of clinical significance. *Cancers (Basel)*. 2021;13(20):5131.
31. Merkies ISJ, Schmitz PIM, Van Der Meché FGA, Samijn JPA, Van Doorn PA. Psychometric evaluation of a new handicap scale in immune-mediated polyneuropathies. *Muscle Nerve*. 2002;25(3):370-377.
32. Dyck PJ, Hughes RAC, O'Brien PC. Quantitating overall neuropathic symptoms, impairments, and outcomes. *Peripheral Neuropathy [Internet]*. Elsevier Inc; 2005:1031-1051. http://www.scopus.com/inward/record.url?scp=84882855831&partnerID=8YFLogxK
33. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2):105-121.
34. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. *J Man Manip Ther*. 2009;17(3):163-170.
35. Vanhoutte EK, Faber CG, Merkies ISJ. 196th ENMC international workshop: Outcome measures in inflammatory peripheral neuropathies 8–10 February 2013, Naarden,The Netherlands. *Neuromuscular Disord*. 2013;23(11):924-933.
36. Kimura J. Principles of nerve conduction studies [internet]. *Electrodiagnosis in Diseases of Nerve and Muscle*. Oxford University Press; 2022. https://oxfordmedicine.com/view/10.1093/med/9780199738687.001.0001/med-9780199738687-chapter-5
37. Drandi D, Genuardi E, Dogliotti I, et al. Highly sensitive MYD88 l265p mutation detection by droplet digital polymerase chain reaction in waldenström macroglobulinemia. *Haematologica*. 2018;103(6):1029-1037.
38. Castillo JJ, Callander NS, Baljevic M, Sborov DW, Kumar S. The evaluation and management of monoclonal gammopathy of renal significance and monoclonal gammopathy of neurological significance. *Am J Hematol*. 2021;96(7):846-853.
39. Latov N. Antibody testing in neuropathy associated with anti-myelin-associated glycoprotein antibodies: where we are after 40 years. *Curr Opin Neurol*. 2021;34(5):625-630.
40. van Schaik IN, Eftimov F, van Doorn PA, et al. Pulsed high-dose dexamethasone versus standard prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT study): a double-blind, randomised, controlled trial. *Lancet Neurol*. 2010;9(3):245-253.
41. Hughes R, Bensa S, Willison H, et al. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol*. 2001;50(2):195-201.
42. Draak THP, Vanhoutte EK, van Nes SI, et al. Comparing the NIS vs. MRC and INCAT sensory scale through Rasch analyses. *J Peripher Nerv Syst*. 2015;20(3):277-288.
43. Delmont E, Hiew FL, Cassereau J, et al. Determinants of health-related quality of life in anti-MAG neuropathy: a cross-sectional multicentre European study. *J Peripher Nerv Syst*. 2017;22(1):27-33.
44. Bourque PR, Masson-Roy J, Warman-Chardon J, et al. Temporal evolution of nerve conduction study abnormalities in anti-myelin-associated glycoprotein neuropathy. *Muscle Nerve*. 2021;63(3):401-404.
45. Ange M, Tang H, Mathis S, et al. Prognostic factor of poor outcome in anti–MAG neuropathy: clinical and electrophysiological analysis of a French Cohort. *J Neurol*. 2019;267:561-571. 10.1007/s00415-019-09618-0
46. Motte J, Fisse AL, Köse N, et al. Treatment response to cyclophosphamide, rituximab, and bortezomib in chronic immune-mediated sensorimotor neuropathies: a retrospective cohort study. *Ther Adv Neurol Disord*. 2021;14:1756286421999631.

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