BRAIN
CLINICAL TRIAL

Rituximab versus placebo for chronic inflammatory demyelinating polyradiculoneuropathy: a randomized trial

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) often requires prolonged ongoing treatment to prevent worsening. The efficacy of rituximab in preventing worsening after the discontinuation of immunoglobulin therapy in patients with CIDP was assessed.

In this randomized, double-blind, placebo-controlled study, conducted at seven Italian hospitals, CIDP patients under immunoglobulin therapy were assigned to receive either rituximab (1 g on Days 1, 15 and 180 ± 7) or placebo. Both groups continued their regular immunoglobulin doses for 6 months post-intervention. The primary end point was the proportion of patients who worsened in any of the following three measures at Month 12, within 6 months after immunoglobulin discontinuation: a decrease of at least one point on the adjusted INCAT score, two points on the MRC sum score, or four points on the RODS centile score. Secondary end points included the proportion of patients deteriorating at Month 18 (within 12 months after immunoglobulin discontinuation), treatment cessation due to adverse events or voluntary reasons, and the time until deterioration after immunoglobulin discontinuation. This study was registered with ClinicalTrials.gov (NCT06325943) and EUDRACT (number 2017-005034-36), and is now complete. From April 2019 to March 2022, 39 patients were recruited; two withdrew consent. The remaining 37 patients were assigned to rituximab ($n = 19$) or placebo ($n = 18$). Median age was 53 (interquartile range 45–64), with 11 (30%) females. A similar proportion of patients in both the rituximab (12/19, 63.2%) and placebo (12/18, 66.6%) groups worsened at Month 12 [odds ratio (OR) 0.86; 95% confidence interval (CI) 0.22–3.32]. No significant differences were noted at Month 18 (OR 0.62; 95% CI 0.14–2.70), or in the mean scores of each scale at Months 6, 12 and 18. The median time to worsening was 5 months for rituximab and 2 months for placebo (Log-rank $P = 0.4372$). Treatment was suspended due to adverse events in one rituximab patient.

In this study, rituximab was not more effective than placebo in preventing clinical deterioration following the discontinuation of immunoglobulin therapy in CIDP. Further studies might evaluate the efficacy of more frequent or earlier administration of rituximab.

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Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a disabling chronic immune-mediated neuropathy with a prevalence ranging from 0.8 to 8.9 cases per 100 000 individuals.[1,2] The majority of CIDP patients improve after therapy with steroids, plasma exchange, intravenous (IVIg) or subcutaneous (SCIg) immunoglobulins with an efficacy ranging from 50–80% of treated patients.[3-7] Most patients require continuous treatment to prevent clinical deterioration, with clinical worsening usually occurring a mean of 4.5 months after IVIg suspension and 14 months after steroid suspension[8] and up to 80% relapsing within 3.5 years from suspension.[8-10] Prolonged treatment increases the cost of immunoglobulin therapy, raises the risk of side effects associated with steroids and the inconvenience associated to repeated courses of plasma exchanges. This has spurred the search for alternative therapies, whose efficacy has been observed in uncontrolled studies but was not confirmed in randomized trials.[11,12]

Rituximab, a chimeric monoclonal antibody that targets the CD-20 antigen on pre-B and mature B cells, reduces the synthesis of new plasma cells and interferes with B cells' antigen-presenting role.[13] The possible efficacy of rituximab in CIDP has been summarized in two reviews showing an improvement in >70% of the patients,[11,14] and in three series of CIDP patients refractory to conventional therapies.[15-17] Uncontrolled studies on patients with autoimmune nodopathy—a demyelinating neuropathy associated with anti-nodal/paranodal antibodies—and not improving after IVIg, also showed a potential benefit of rituximab.[18-20]

We performed a phase 2, multicentre, randomized, placebo-controlled study to determine the efficacy of rituximab in preventing clinical deterioration after immunoglobulin discontinuation in patients with CIDP.

Materials and methods

Study design

This was a multicentre, randomized, double-blind, placebo-controlled study in patients with CIDP under chronic effective treatment with IVIg or SCIg. The study was conducted at seven hospitals in Italy. The trial protocol and the subsequent amendments were approved by the ethics committees of all participating centres. The trial is registered with ClinicalTrials.gov (ID: NCT06325943), EUDRACT number 2017-005034-36, and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before participation in any trial-related procedures. The reporting of the study adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Patients

Patients with a documented diagnosis of definite or probable CIDP according to the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria were recruited.[21] Eligibility required documented improvement after initial immunoglobulin therapy and ongoing (minimum of 6 months) effective maintenance therapy with IVIg or SCIg prior to study entry. Clinically meaningful treatment improvement was defined as a change of at least one point on the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) score, two points on the Medical Research Council (MRC) sum score, or four points on the Inflammatory Rasch-built Overall Disability Scale (I-RODS) centile score.[22] Additional inclusion criteria included the following: (i) age 18 years or older; (ii) Ig-dependency confirmed by clinical examination in the 12 months before screening, with a clinically relevant worsening (as defined by the aforementioned criteria) after IVIg reduction or withdrawal; (iii) stable SCIg or IVIg dosage (not exceeding ±20% deviation) and frequency for at least 3 months prior to enrolment, corresponding to once or twice weekly ±2 days for SCIg, or every 2 to 8 weeks ±5 days for IVIg, with clinical stability between doses; (iv) possible steroid use up to a maximum of 12.5 mg/day or 25 mg on alternate days of prednisone, or pulsed methylprednisolone at 400 mg/monthly, provided the dosage had been stable (± 20%) in the previous 6 months and remained unchanged during the study; (v) female subjects of childbearing potential were required to provide a negative serum pregnancy test and use a highly effective contraceptive method throughout the study and for 12 months following the last drug dose; and (vi) male subjects

with partners of childbearing potential had to be willing to use a highly effective contraceptive method for the same period. Exclusion criteria included: (i) current diagnosis or history of type 1 or type 2 diabetes mellitus; (ii) IgM paraprotein with anti-myelin-associated glycoprotein (MAG) antibodies; (iii) multifocal motor neuropathy; (iv) CIDP relapse or significant worsening within 6 months before randomization; (v) clinical or known evidence of other medical conditions that might cause neuropathy; (vi) pregnant or lactating females; (vii) any medical or psychiatric condition that could compromise the ability to participate in the study; (viii) congestive heart failure or moderate-to-severe impairment of cardiac function; (ix) renal or liver impairment defined by serology tests; (x) leukopenia, lymphopenia or platelet count <100 000/mm^3; (xi) history or serological evidence of clinically relevant ongoing chronic or active infections or hospitalization for infection within 6 weeks prior to the first dose of rituximab; (xii) family history of primary immunodeficiency; (xiii) active neoplastic disease or within 5 years before study entry, except for definitively treated skin basal or squamous cell carcinoma or carcinoma *in situ* of the uterine cervix; (xiv) treatment with plasma exchange or immune absorption within 3 months before randomization, immune suppressive or chemotherapeutic medications within 6 months before randomization, mitoxantrone, alemtuzumab, cladribine at any time, total lymphoid irradiation or haematopoietic stem cell transplantation at any time, any biological therapy within 12 months before randomization; (xv) administration of a live vaccination within 8 weeks before the baseline visit, or its planning during the study, or within 7 weeks after the final dose of rituximab; (xvi) prior rituximab treatment within 12 months before inclusion; and (xvii) history of hypersensitivity to any of the study drugs or of similar chemical classes.

Randomization and masking

Eligible patients were randomized in a 1:1 ratio to receive either rituximab or placebo, using a computer-generated procedure balanced across centres. An unblinded pharmacist prepared the treatment solution separately from where the patient was treated. Trial drugs were transferred in identical blind bottles, labelled with the patient's identification number, and delivered to the trial nurse, who was blind to treatment allocation. For emergency unblinding, sealed envelopes containing the assigned product's name were held at each centre, to be opened only in case of a serious adverse reaction. Blinding of the treatment identity was maintained for patients, investigators, assessors and data analysts until the database lock. This was ensured by: (i) maintaining the confidentiality of randomization data, which was not accessible to anyone except in medical emergencies prior to database lock; and (ii) the use of identical-looking study drugs for both physicians and patients.

Procedures

Following the rheumatoid arthritis treatment protocol,[23] patients received 1 g of rituximab intravenously or a placebo on Days 1 and 15 (1 week before and 1 week after the first immunoglobulin infusion in the study), and at 6 months (180 ± 7, 1 week after the final immunoglobulin infusion) post-randomization.

Pre-medication included 1 g of oral paracetamol, 10 mg of chlorphenamine maleate and 125 mg of methylprednisolone, diluted in 100 ml of sodium chloride solution and infused over 20 min, at least 30 min prior to each infusion. All patients continued their established doses of IVIg or SCIg for 6 months following the first dose of rituximab/placebo. Participants who experienced objective deterioration or who reported feeling worse, requesting to exit the study, were considered treatment failures. They were withdrawn from the study and received an IVIg dose of 2 g/kg over 4–5 days, followed by the maintenance dose previously established prior to therapy cessation.

Evaluation protocols

Evaluation before inclusion

Each patient underwent assessment at the hospital within 30 days prior to treatment initiation by: (i) complete neurological examination; (ii) internal medicine evaluation with ECG, blood pressure (BP) measurement and chest X-ray; (iii) blood chemistry and haematology tests, including complete blood cell count, urea, creatinine, glucose, erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma GT, alkaline phosphatase, bilirubin, Na+, K+, Ca++, serum protein electrophoresis, anti-HCV antibodies, anti-HIV1 and HIV2 antibodies, HBsAg, anti-HbcAb, anti-HbsAb and blood lymphocyte subpopulation including CD19; (iv) serum pregnancy test for females; (v) CSF examination if not previously conducted and if needed to support the diagnosis[21,22]; (vi) neurophysiological evaluation of motor median, ulnar, peroneal and tibial nerves, and of sensory ulnar and sural nerves; (vii) muscle strength assessment on 12 muscles using the MRC scale[24] (range of 0–60, with 0 indicating most impairment); (viii) disability assessment with the INCAT scale[25] (ranges 0 to 10, with 10 indicating most impairment), and the I-RODS[26] (ranges 0 to 48, with 0 indicating most impairment); and (ix) quality of life assessment using the 36-Item Short Form Health Survey questionnaire (SF-36).[27]

Evaluation during the study

Pre-infusion samples were collected on the day of the second and third rituximab/placebo infusions to analyse red and white blood cells, platelet, lymphocytes and neutrophil counts, and to evaluate AST, ALT, gamma GT, creatinine, blood urea, Na+, K+ and Ca++, and lymphocyte subpopulation. Following the initial assessment, patients were re-examined at the hospital before the first and the second infusion of rituximab/placebo, and subsequently at Months 2, 4, 6, 8, 10, 12, 15 and 18, as well as at times of CIDP worsening or when the patient opted to resume immunoglobulin therapy. Assessment included: (i) evaluation of therapy side effects, with recording of vital signs and any concurrent diseases, disorders or treatments; (ii) the MRC sum scale, INCAT and I-RODS disability scales, with the SF-36 assessed at Months 6, 12 and 18 post-treatment; (iii) electroneurographic evaluation of the two most diagnostic nerves at Month 6, and a complete evaluation at Month 12; (iv) comprehensive haematology and chemistry blood tests (as detailed previously) at Months 2, 4, 6 and 12 post-treatment; (v) a serum pregnancy test before the last dose of rituximab; (vi) a blood lymphocyte subpopulation count after 2, 6 (before rituximab/placebo infusion) and 12 months; and (vii) BP evaluation before and after each infusion of rituximab/placebo.

Outcomes

The primary end point of the study was the difference in the proportion of patients who experienced a deterioration in any of the following three measures at Month 12, within 6 months after immunoglobulin discontinuation: ≥1-point on the adjusted INCAT score, ≥2 points on the MRC sum-score, or ≥4 points on the

I-RODS centile score. The decision to use three different outcome measures to define clinical improvement aligns with the 2021 EAN/PNS guidelines for CIDP,[22] which propose various clinically meaningful change criteria, all of which have been utilized in previous clinical trials.

Secondary end points included: (i) the difference in the mean change in the adjusted INCAT, I-RODS centile, and MRC scores at Months 6, 12 and 18 post-treatment compared to baseline in the rituximab and placebo arms; (ii) the difference in the proportion of patients who worsened by ≥1 point in the adjusted INCAT score or ≥2 points in the MRC sum score or ≥4 points in the I-RODS centile score at Month 18, within 12 months post-immunoglobulin discontinuation; (iii) the difference in the proportion of patients who had suspended treatment for adverse events (AEs) or voluntary reasons in the 12 months following the start of treatment; (iv) the difference in the cumulative probability of worsening after immunoglobulin discontinuation; and (v) the difference in the mean variation compared to the baseline in quality of life measured by the SF-36 scale at Months 6, 12 and 18.

Exploratory end points included: (i) the mean variation of motor conduction block, negative distal compound muscle action potential (CMAP) amplitude, motor conduction velocity, distal and F-wave latencies in the median, ulnar, tibial and peroneal nerves between baseline and Months 12 and 18 in the rituximab and placebo groups; (ii) the response to therapy in relation to the clinical form of typical CIDP or its variants; and (iii) the response to therapy in relation to the presence of anti-nodal/paranodal antibodies.

Antibody testing

All the sera were tested before treatment for the presence of anti-nodal/paranodal antibodies by ELISA using recombinant Neurofascin (NF) 155 protein (OriGene RC228652) or Contactin (CNTN) 1 protein (OriGene RC214706) or NF186 protein (TP 329070 Origene) or Contactin-Associated Protein (Caspr) 1 protein (2418-CR R&D). Results were verified by cell-based assay on transfected human embryonic kidney (HEK) 293 at the Hospital de la Santa Creu in Barcelona.[18]

Statistical analysis

Sample size calculation

Given that ~50% of CIDP patients relapse within 6 months of IVIg discontinuation (median time to deterioration being 4.5 months in one study[8] and 45% worsening by 6 months in another[9]) it was estimated that 38 patients (19 in each group) were needed to detect a 40% absolute reduction in the proportion of patients worsening after immunoglobulin discontinuation in the experimental arm, with 80% power and 5% significance level using a one-side chi-square test. This sample size was also supported by two uncontrolled studies showing ~10% worsening rate after rituximab therapy.[15,16]

Statistical analysis plan

Primary efficacy analyses were conducted on the intention-to-treat population, including all participants who received at least one dose of the study medication. Per-protocol analyses for those with protocol deviations were also planned but not executed as only one patient had a deviation. Demographic and clinical variables at study entry were described using medians with interquartile ranges (IQRs) for continuous variables, and frequencies and percentages for categorical variables, reported by treatment group. Comparisons used the Wilcoxon-Mann-Whitney test for continuous variables and the chi-square or Fisher's exact test for categorical variables. For the primary end point, the proportion of participants worsening at Month 12, 6 months post-immunoglobulin discontinuation was assessed for each group. Odds ratios (ORs) for worsening, with 95% confidence intervals (CIs), were calculated using a univariable logistic regression model, with treatment as the independent variable and worsening as the dependent variable, and comparisons made using the Wald test. A multivariable logistic regression model adjusted for any unbalanced variables between groups was used to calculate adjusted ORs and 95% CIs. Secondary end points (i) and (v) were analysed with repeated measures linear mixed models using an unstructured variance-covariance matrix. The model separately incorporated the total scores of adjusted INCAT, MRC, I-RODS centiles, and SF-36 score—which includes eight different domains and two indexes for physical and mental components—as dependent variables. Treatment, time (in months), and their interaction were included as independent variables. These models estimated mean scores for each treatment group at each time point (Months 0, 6, 12, 18), differences between treatment groups at each time point, and changes within each group over 6 months (slopes).

The treatment effect was quantified in terms of difference in the variation over time between the two groups (difference between the slopes) and was tested by the treatment-time interaction term. Differences within treatment groups were tested by the time main effect, while the treatment main effect was used to identify differences in the estimated mean scores at baseline (Month 0). Secondary end points (ii) and (iii) were analysed using the same methods described for the primary end point. Secondary end point (iv) was assessed with Kaplan-Meier survival curves, with worsening as event variable, and time from immunoglobulin suspension to worsening as time variable; treatment groups were compared with the log-rank test. Exploratory end point (i) was evaluated using a repeated measures linear mixed model, similar to end points (i) and (v). The dependent variables in this model included motor conduction block (measured as the ratio of proximal to distal CMAP multiplied by 100), negative distal CMAP amplitude, motor conduction velocity, and distal and F-wave latencies across the median, ulnar, tibial and peroneal nerves. Exploratory end points (ii) and (iii) were analysed similarly to the primary end point, stratifying patients by clinical form (typical CIDP or its variants) and antibody reactivity.

Results

Of 48 patients screened, 11 (23%) were excluded and 37 (77%) underwent randomization (Fig. 1) between April 2019 and March 2022. Screening failure was most commonly due to exclusion criteria such as relevant medical history ($n = 4$), positive hepatitis serology ($n = 2$) or incompatible cardiac medication ($n = 1$). Two patients withdrew consent prior to treatment. Of the 37 patients included in the analyses, 24 were receiving IVIg and 13 SCIg as effective maintenance treatment. Median age was 53 years (IQR 45–64) and 11 participants (30%) were female. Nineteen patients were assigned to rituximab and 18 to placebo.

Demographic and clinical features at entry are detailed in Table 1. All but one patient in the placebo group had a definite CIDP diagnosis versus all patients in the rituximab group. Diagnoses included typical CIDP (31 patients), multifocal CIDP ($n = 5$; 2 placebo group, 3 rituximab) and motor CIDP ($n = 1$ in the rituximab group). Patients in the rituximab group had a longer disease duration (6.1 years versus 3.4 years) and higher baseline MRC

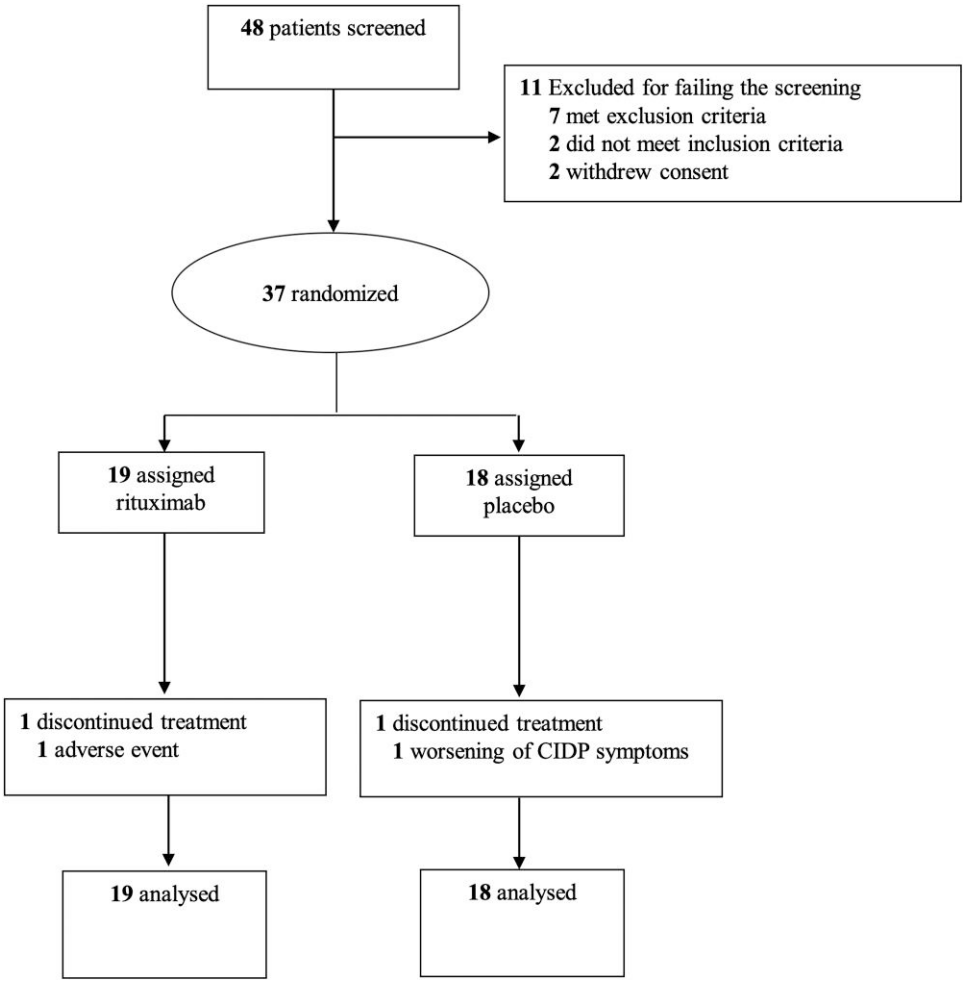

Figure 1 Study diagram. CIDP = chronic inflammatory demyelinating polyradiculoneuropathy.

score (median 54 versus 57) but reported superior quality of life metrics. None exhibited anti-node/paranode antibodies at entry. Three patients (16%) in the rituximab group and one (6%) in the placebo group were receiving oral prednisone before inclusion and continued the same dosage during the study.

The same proportion of patients relapsed at Month 12, within 6 months after therapy discontinuation, in both the rituximab (12/19; 63.2%) and placebo (12/18; 66.7%) groups (OR 0.86; 95% CI 0.22–3.32) (Table 2), with no significant differences upon adjusting for disease duration and baseline MRC sum score (adjusted OR 1.15; 95% CI 0.23–5.82) and steroid use (adjusted OR 0.88; 95% CI 0.16–4.88). By Month 18, within 12 months after therapy discontinuation, the proportions were 68.4% (13/19) for rituximab and 77.8% (14/18) for placebo (OR 0.62; 95% CI 0.14–2.70), with the adjusted outcome also showing no statistical significance (adjusted OR 0.59; 95% CI 0.09–3.71) (Table 2). When the analyses were repeated, evaluating worsening in at least two outcome measures, there was still no statistically significant difference between the two groups (OR 1.5; 95% CI 0.22–10.40). Similarly, no significant difference was found when the analyses was repeated considering a four point decrease as the threshold for change on the MRC sum score (OR 0.86; 95% CI 0.22–3.32). In none of the patients was relapse captured by all three outcome measures simultaneously.

Disability and impairment trajectories, quantified via INCAT, I-RODS and MRC total scores, demonstrated no significant intergroup differences across the study period (Supplementary Table 1), indicating that rituximab did not modify disease progression, as assessed by these scales. The change in the adjusted INCAT score during the study, compared to baseline, was not significant ($P = 0.3420$), with an estimated increase of 0.166 points every 6 months in the placebo group and 0.141 in the rituximab group. No difference was observed between the two groups in the change of the adjusted INCAT score during the follow-up, with a difference in the slopes between rituximab and placebo of −0.024 (95% CI −0.651; 0.603; $P = 0.9396$). The estimated variation of the I-RODS centile score during the follow-up compared to baseline was also not significant ($P = 0.8789$), with an increase of 0.649 every 6 months in the placebo group and a reduction of −1.151 in the rituximab group, without significant differences between the two groups (difference in the slopes: −1.800; 95% CI −8.248; 4.649; $P = 0.5829$). The same was observed for the MRC sum score: the estimated variation during the follow-up compared to baseline was not significant ($P = 0.8559$), with an increase of 0.308 every 6 months in the placebo group and a decrease of −0.154 every 6 months in the rituximab group. The difference in slopes was not significant (rituximab versus placebo: −0.462; 95% CI −2.116; 1.191; $P = 0.5825$).

Quality of life analysis using the SF36 revealed that despite higher baseline scores in the rituximab group on some parameters, there was no significant temporal change in any of the parameters, nor were there significant differences between treatment groups

Table 1 Demographic and clinical features of treated patients at entry

	Placebo (*n* = 18)	Rituximab (*n* = 19)	*P*-value
Gender, *n* (%)	–	–	0.2963
Female	7 (39)	4 (21)	
Male	11 (61)	15 (79)	
EFNS/PNS category, *n* (%)	–	–	0.4865
Definite	17 (94)	19 (100)	
Probable	1 (6)	0 (0)	
CIDP clinical form, *n* (%)	–	–	0.6599
CIDP variant	2 (11)	4 (2)	
Typical	16 (89)	15 (79)	
CIDP variant form, *n* (%)	–	–	>0.9999
Multifocal	2 (11)	3 (16)	
Motor	NA	1 (5)	
Therapy, *n* (%)	–	–	0.3615
IVIg	13 (72)	11 (58)	
SCIg	5 (28)	8 (42)	
IVIg/SCIg dosage, g/kg/week, median (range)	0.25 (0.1–0.9)	0.28 (0.1–0.8)	0.9021
IVIg frequency	–	–	0.1484
Every 2–4 weeks	10 (77)	7 (64)	
Every 5–8 weeks	3 (23)	4 (36)	
Anti-nodal/paranodal antibodies	0	0	
	Median (IQR)	**Median (IQR)**	
Age at diagnosis	51 (44–61)	42 (31–52)	0.0743
Age at randomization	54 (4–65)	49 (37–63)	0.3015
Disease duration, years	3 (2–6)	6 (4–11)	0.0209
Diagnostic delay	9 (3–30)	8 (2–13)	0.4613
INCAT	2 (1–3)	3 (2–4)	0.2365
RODS	34 (28–43)	36 (32–41)	0.5827
MRC	57 (56–60)	54 (50–58)	0.0258
SF36	–	–	
Physical functioning	57 (40–70)	65 (45–75)	0.5717
Role physical index	0 (0–100)	50 (50–75)	0.0411
Body pain	52 (41–100)	84 (42–100)	0.2864
General health perceptions	48 (32–67)	52 (37–62)	>0.9999
Vitality	47 (40–65)	60 (45–70)	0.3876
Social functioning	75 (50–87)	75 (50–87)	0.7989
Role emotional index	33 (0–100)	100 (67–100)	0.0110
Mental health index	70 (52–80)	74 (48–88)	0.4325
Standardized Physical Component Scale	34 (32–39)	40 (36–42)	0.1419
Standardized Mental Component Scale	48 (37–54)	52 (43–57)	0.1502

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society; INCAT = Inflammatory Neuropathy Cause and Treatment; IQR = interquartile range; IVIg = intravenous immunoglobulin; MRC = Medical Research Council; NA = not applicable; RODS = Rasch-built Overall Disability Scale; SCIg = subcutaneous immunoglobulin; SF36 = Short Form Health Survey-36.

across any domain or in the standardized physical and mental component scales (Supplementary Table 2).

Figure 2 depicts the cumulative probability of worsening over time following the discontinuation of immunoglobulin in patients receiving rituximab versus placebo. Median time to relapse was 5 months (IQR 2.3 to not estimable) in the rituximab group compared to 2 months (IQR 1.4–12.0) in the placebo group. At Month 8, 2 months after immunoglobulin discontinuation, the cumulative probability of relapse was lower in the rituximab group (22%) than in the placebo group (47%). This difference persisted at Month 10, 4 months after discontinuation (39% rituximab versus 59% placebo). By Month 12, 6 months after discontinuation, the gap narrowed and the Kaplan-Meier curves showed no significant difference between the groups (Log-rank $P = 0.4372$).

Two patients did not complete the 6-month treatment course: one developed severe, diffuse petechial erythema on limbs and trunk, along with wrist and ankle swelling and high fever (39°C)

Table 2 Worsening at Months 12 and 18 (6 and 12 months post-immunoglobulin therapy discontinuation)

	Placebo (*n* = 18)	Rituximab (*n* = 19)
Worsening at Month 12 (primary end point)		
n	12 (67%)	12 (63%)
OR 95% CI	–	0.86 (0.22–3.32)
P-value	–	0.8232
Adjusted OR, 95% CI	–	1.15 (0.23–5.82)
P-value	–	0.8620
Worsening at Month 18 (secondary end point)		
n and percentage	14 (78%)	13 (68%)
OR, 95% CI	–	0.62 (0.14–2.70)
P-value	–	0.5235
Adjusted OR 95% CI	–	0.59 (0.09–3.71)
P-value	–	0.5742

CI = confidence interval; OR = odds ratio.

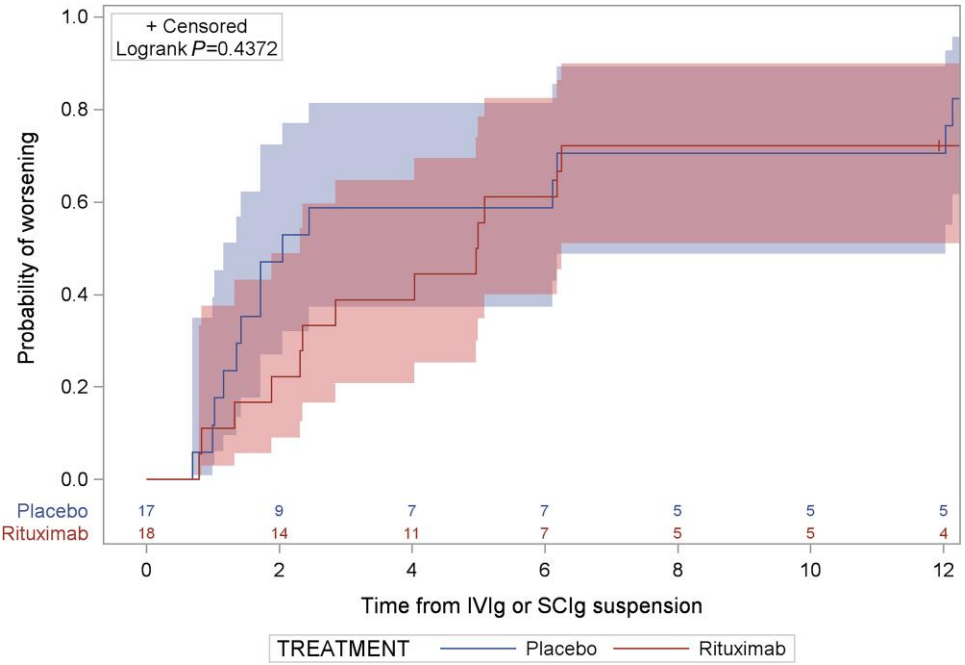

Figure 2 Cumulative probability of worsening after immunoglobulin discontinuation in the rituximab and placebo groups. The figure displays the cumulative probability of relapse in the rituximab and placebo groups following discontinuation of immunoglobulin therapy. Time is measured in months. Shaded bands represent 95% confidence intervals. The number of patients at risk in each treatment group at each time point is shown below the x-axis. IVIg = intravenous immunoglobulins; SCIg = subcutaneous immunoglobulins.

Table 3 Results of CD19+ examinations at entry and during the study

Time point	Group	Mean (%)	Range	CD19 > 0 (%)
Screening	Rituximab	9.22	3.00–20.00	18/18 (100%)
	Placebo	11.14	6.00–18.00	15/15 (100%)
Month 2	Rituximab	1.06	0.00–15.00	2/17 (12%)
	Placebo	10.55	4.00–18.00	13/13 (100%)
Month 6	Rituximab	1.86	0.00–6.00	12/17 (71%)
	Placebo	11.47	3.91–24.00	14/14 (100%)
Month 12	Rituximab	1.70	0.00–6.00	12/15 (80%)
	Placebo	10.36	4.30–20.00	14/14 (100%)

11 days after the first rituximab infusion. This patient was treated in the emergency room with intravenous methylprednisolone, amoxicillin and chlorphenamine maleate, and discharged 2 days later following symptom resolution. The other experienced severe clinical worsening 5 months after initiating placebo, despite ongoing IVIg therapy. Both were withdrawn but monitored until Month 6. One rituximab-treated patient worsened at Month 5 due to an unexpected IVIg treatment delay but recovered after resuming IVIg at Month 6. A higher proportion of rituximab-treated patients (47.4%) experienced at least one adverse event within 12 months versus the placebo group (27.8%), though this difference was not statistically significant ($P = 0.2194$). Details on AE severity, their relationship with the study drug, serious AEs and AEs leading to treatment discontinuation are provided in Supplementary Table 3.

Differences in haematological parameters between groups were noted only in CD19 counts, which significantly decreased ($P < 0.001$) in the rituximab group at Months 2, 6 and 12 (Table 3 and Supplementary Table 4). More patients showed absent CD19+ cells at Month 2 ($n = 15$) compared to Month 6 ($n = 5$) and Month 12 ($n = 3$) (Table 3). At Month 8, within 2 months after therapy discontinuation, 1 out of 15 (7%) patients with CD19 = 0 relapsed, while none (0/2) with CD19 > 0 relapsed. The corresponding relapse rates at Month 12, within 6 months after discontinuation, were 0/5 for CD19 = 0 patients and 2/12 (17%) for CD19 > 0 patients. At Month 18, relapse occurred in 2/3 (67%) of CD19 = 0 patients and 7/12 (58%) of CD19 > 0 patients. Differences in relapse rates between CD19 = 0 and CD19 > 0 groups were not statistically significant.

No significant differences were observed in the mean variation of nerve conduction study parameters across nerves from treatment start to Months 6 and 12, nor in the slope of changes between the two groups (Supplementary Table 5).

The majority of patients had typical CIDP (31/37) and their treatment response was consistent with the entire cohort: 66.7% in the rituximab group worsened by Months 12 and 18, compared to 75% and 81.3% in the placebo group, without significant differences between treatment groups (Supplementary Table 6). Among the six patients with CIDP variants, 50% of the four patients treated with rituximab deteriorated at Month 12 and 75% at Month 18, while none worsened by Month 12 and one by Month 18 in the placebo group. The small number of patients in this subgroup precluded reliable statistical analysis (Supplementary Table 6).

An additional subgroup analysis examined relapse rates in rituximab-treated patients with disease durations below or at/above the median (6 years). At Month 12, relapse rates were 67% (6/9) in the shorter duration group and 60% (6/10) in the longer duration group, and by Month 18, 78% (7/9) and 60% (6/10), respectively. Differences between groups were not statistically significant.

Discussion

In this double-blind randomized controlled study, no significant difference was found between patients treated with rituximab or

placebo regarding the proportion and time to relapse at Months 12 and 18, within 6 and 12 months after discontinuation of effective immunoglobulin therapy. No significant differences in the other outcomes were observed between the two groups of patients either. Additionally, no patients tested positive for anti-node/paranode antibodies at entry; thus, this study provides no data on the role of rituximab in patients with autoimmune nodopathies. Rituximab was well tolerated, with only one patient discontinuing the therapy due to a serious AE that was possibly related to an allergic reaction to the drug.

A non-significant increase in the median time to deterioration was noted, with rituximab-treated patients experiencing a median of 5 months to relapse compared to 2 months in those treated with placebo. There was a 25% absolute reduction in the proportion of patients worsening at Month 8 and 20% at Month 10 (2 and 4 months, respectively, after discontinuation of effective immunoglobulin therapy). However, these differences vanished by Month 12 (6 months after discontinuation) and remained absent throughout the follow-up period.

A similar 26% difference at 6 months was noted in the PATH study[6] between low-dose SCIg and placebo, where the larger sample size revealed a significant difference. The sample size for our study was determined based on the findings from two previous studies,[8,9] which, however, differed in inclusion criteria, outcome measures and sample size. In one study, 21% of patients were receiving concomitant azathioprine or steroid therapy, and the outcome measures included the overall neuropathy limitation scale (ONLS) and the modified Rankin scale (mRS).[8] In the other study, patients with an INCAT disability score >2 were included, and the primary end point was based on the INCAT disability scale.[9] Notably, the proportion of patients experiencing relapse at 6 months following IVIg discontinuation was higher in our study compared to these prior studies.

In this study, non-zero CD19 levels at Months 12 and 18 suggest that additional doses of rituximab might have given greater benefit. Our decision to assess the response to rituximab at Months 12 and 18 (6 and 12 months, respectively, after discontinuation of immunoglobulin therapy) was informed by previous studies of rituximab in anti-MAG antibody neuropathy.[28,29] It is also possible that immune reactivity in our patients, treated on average of 6.1 years after disease onset, had stabilized, resulting in a plasma cell pool less responsive to rituximab. For instance, early treatment efficacy with rituximab is documented in conditions like myasthenia gravis,[30] optic neuromyelitis[31] and pemphigus.[32]

Our study did not confirm the efficacy of rituximab seen in previous uncontrolled studies on CIDP patients unresponsive to IVIg or other standard immune therapies,[15-17] or in those with autoimmune nodopathies.[18-20] This discrepancy might reflect different pathogenic mechanisms in immunoglobulin responsive patients. Confirming the efficacy of rituximab in these populations, however, requires randomized study.

This study has some limitations. First, the small sample size. The trial was designed to detect only a large difference between groups, making it possible that a larger sample size could have altered the results. Despite multicentre collaboration,[7,8,17] recruitment proved difficult due to the low prevalence of the disease and the reluctance of investigators and patients to discontinue effective immunoglobulin treatment for an unproven drug or placebo. Only patients receiving treatment were eligible, excluding treatment-naïve individuals, which further narrowed the pool of potential participants. It was ethically untenable to test an unproven treatment on untreated patients, and difficult to identify participants who required ongoing treatment to prevent deterioration. Second, the study design does not allow to exclude the potential efficacy of earlier or more frequent rituximab treatment in CIDP, as observed in other diseases. Third, the imbalance at baseline in certain parameters between the two groups, including disease duration, may have negatively impacted the remission rate for rituximab, as longer disease duration has previously been associated with a higher likelihood of IVIg dependency.[33,34] Fourth, the trial was not designed to assess the long-term safety of rituximab in patients with CIDP. Additionally, despite the trial design targeting active disease, ~20–30% of participants, consistent with previous studies,[6,12] did not experience a confirmed worsening event 12 months post-immunoglobulin discontinuation, suggesting possible remission. Finally, the study excluded patients on maintenance steroid therapy, except for those receiving a maximum dose of 12.5 mg/day of prednisone, which may limit the generalizability of the findings. This exclusion was based on the typically longer interval before relapse observed after discontinuing steroid therapy, compared to the shorter relapse interval following the discontinuation of intravenous immunoglobulin.[8-10]

In conclusion, in this randomized placebo-controlled trial, rituximab did not demonstrate greater efficacy than placebo in preventing clinical deterioration following the discontinuation of immunoglobulin therapy in CIDP. Future studies are warranted to explore the efficacy of treatment with rituximab in CIDP either earlier in the disease course or more frequently.

Data availability

Anonymized data used for this study are available upon reasonable request from the corresponding author.

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Competing interests

E.N.O. reports personal fees for Advisory or Scientific Board from ArgenX (Belgium), Dianthus (USA); Janssen (USA), LFB (France), Longboard Pharma (USA), Sanofi (USA), Janssen (USA), for lecturing from CSL-Behring (Italy). Received a research grant from Baxalta/Takeda, USA, on Multifocal Motor Neuropathy, from Agenzia Italiana del Farmaco (AIFA) and from GBS/CIDP Foundation International. He received travel grants to attend scientific meetings from Kedrion (Italy). F.M. reports honoraria for lectures from Alnylam, Alfa Sigma, and SOBI. G.L.P. has received travel grants to attend scientific meetings from CSL Behring (Italy) and Kedrion

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Supplementary material

Supplementary material is available at *Brain* online.

References

1. Lehmann HC, Burke D, Kuwabara S. Chronic inflammatory demyelinating polyneuropathy: Update on diagnosis, immunopathogenesis and treatment. *J Neurol Neurosurg Psychiatry*. 2019;90:981-987.
2. Lunn MPT, Manji H, Choudhary PP, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: A prevalence study in south east England. *J Neurol Neurosurg Psychiatry*. 1999;66:677-680.
3. Hughes RA, Mehndiratta MM, Rajabally YA. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev*. 2017;11:CD002062.
4. Mehndiratta MM, Hughes RA, Agarwall P. Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev*. 2015;2015:CD003906.
5. Bus SR, de Haan RJ, Vermeulen M, et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev*. 2024;2:CD001797.
6. van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2018;17:35-46.
7. Nobile-Orazio E, Cocito D, Jann S, et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: A randomised controlled trial. *Lancet Neurol*. 2012;11:493-502.
8. Nobile-Orazio E, Cocito D, Jann S, et al. Frequency and time to relapse after discontinuing 6-month therapy with IVIg or pulsed methylprednisolone in CIDP. *J Neurol Neurosurg Psychiatry*. 2015;86:729-734.
9. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): A randomised placebo-controlled trial. *Lancet Neurol*. 2008;7:136-144.
10. Eftimov F, Vermeulen M, van Doorn PA, et al. Long-term remission of CIDP after pulsed high-dose dexamethasone or short-term prednisolone treatment. *Neurology*. 2012;78:1079-1084.
11. Mahdi-Rogers M, Brassington R, Gunn AA, et al. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev*. 2017;5:CD003280.
12. Hughes R, Dalakas MC, Merkies I, et al. Oral fingolimod for chronic inflammatory demyelinating polyradiculoneuropathy (FORCIDP trial): A double-blind, multicentre, randomised controlled trial. *Lancet Neurol*. 2018;17:689-698.
13. Pescovitz MD. Rituximab, an anti-CD20 monoclonal antibody: History and mechanism of action. *Am J Transplant*. 2006;6:859-866.
14. Hu J, Sun C, Lu J, et al. Efficacy of rituximab treatment in chronic inflammatory demyelinating polyradiculoneuropathy: A systematic review and meta-analysis. *J Neurol*. 2022;269:1250-1263.
15. Muley SA, Jacobsen B, Parry G, et al. Rituximab in refractory chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve*. 2020;61:575-579.
16. Fatehi F, Okhovat AA, Panahi A, et al. Retrospective analysis of response to rituximab in chronic inflammatory demyelinating polyneuropathy refractory to first-line therapy. *J Peripher Nerv Syst*. 2021;26:469-474.
17. Doneddu PE, Cocito D, Fazio R, et al. Prospective open-label trial with rituximab in patients with chronic inflammatory demyelinating polyradiculoneuropathy not responding to conventional immune therapies. *J Neurol Neurosurg Psychiatry*. 2024;95:838-844.
18. Querol L, Rojas-García R, Diaz-Manera J, et al. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. *Neuroimmunol Neuroinflamm*. 2015;2:e149.
19. Vural A, Doppler K, Meinl E. Autoantibodies against the node of ranvier in seropositive chronic inflammatory demyelinating polyneuropathy: Diagnostic, pathogenic, and therapeutic relevance. *Front Immunol*. 2018;9:1029.
20. Liu B, Hu J, Sun C, et al. Effectiveness and safety of rituximab in autoimmune nodopathy: A single-center cohort study. *J Neurol*. 2023;270:4288-4295.
21. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *J Peripher Nerv Syst*. 2010;15:1-9.
22. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force-Second revision. *Eur J Neurol*. 2021;28:3556-3583.
23. Edwards JCW, Szczepanski L, Szechinski J, et al. Efficacy of B-cell–targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med*. 2004;350:2572-2581.
24. Kleyweg RP, van der Meche FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. *Muscle Nerve*. 1991;14:1103-1109.
25. Merkies IS, Schmitz PI, van der Meche FG, et al. Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies. *J Neurol Neurosurg Psychiatry*. 2002;72:596-601.
26. van Nes SI, Vanhoutte EK, van Doorn PA, et al. Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. *Neurology*. 2011;76:337-345.
27. Ware JE Jr, Sherbourne CD. The MOS 36-item short form health survey (SF-36): I: Conceptual framework and item selection. *Med Care*. 1992;30:473-483.
28. 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;65:286-293.
29. Leger JM, Viala K, Nicolas G, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. *Neurology*. 2013;80:2217-2225.

30. Piehl F, Eriksson-Dufva A, Budzianowska A, et al. Efficacy and safety of rituximab for new-onset generalized myasthenia Gravis. The RINOMAX randomized clinical trial. *JAMA Neurol*. 2022;79:1105-1112.
31. Park SY, Kwon YN, Kim S, et al. Early rituximab treatment reduces long-term disability in aquaporin-4 antibody-positive neuromyelitis optica spectrum. *J Neurol Neurosurg Psychiatry*. 2023;94:800-805.
32. Nosrati A, Mimouni T, Hodak E, et al. Early rituximab treatment is associated with increased and sustained remission in pemphigus patients: A retrospective cohort of 99 patients. *Dermatol Ther*. 2022;35:e15397.
33. Rabin M, Mutlu G, Stojkovic T, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: Search for factors associated with treatment dependence or successful withdrawal. *J Neurol Neurosurg Psychiatry*. 2014;85:901-906.
34. Rajabally YA, Min YG, Nazeer KK, Englezou C. Treatment response amplitude and timing in chronic inflammatory demyelinating polyneuropathy with routine care: Study of a UK cohort. *Eur J Neurol*. 2024;31:e16399.