Received: 24 June 2022 | Revised: 22 October 2022 | Accepted: 25 October 2022

DOI: 10.1002/mus.27746

CLINICAL RESEARCH SHORT REPORTS

MUSCLE&NERVE WILEY

CIDP prognosis in patients with IVIG treatment-related fluctuations

Melissa Cook MD[1] | Mamatha Pasnoor MD[2] | Senda Ajroud-Driss MD[3] | Thomas H. Brannagan MD[4] | Mazen M. Dimachkie MD[2] | Jeffrey A. Allen MD[1]

[1]Department of Neurology, University of Minnesota, Minneapolis, Minnesota, USA

[2]Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas, USA

[3]Department of Neurology, Northwestern University, Chicago, Illinois, USA

[4]Department of Neurology, Columbia University Vagelos College of Physicians and Surgeons, New York, New York, USA

Correspondence
Jeffrey A. Allen, Department of Neurology, University of Minnesota, 12-150 Phillips Wangensteen Building, 516 Delaware Street SE, Minneapolis, MN 55455, USA.
Email: jaallen@umn.edu

Abstract

Introduction/aims: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired immune-mediated peripheral nerve disorder with variable prognosis and long-term dependence on immunotherapy. Frequent assessment of grip strength can be a useful tool to identify intravenous immunoglobulin (IVIG) treatment-related fluctuations (TRFs) and optimize IVIG treatment in real-time, but the long-term implications of TRFs are unknown. We aimed to explore the impact that real-time TRFs had on long-term CIDP prognosis, strength impairment, and disability.

Methods: This retrospective observational cohort study analyzed standard of care clinical and treatment outcomes in patients who participated in a published prospective study of intra-IVIG-cycle grip strength quantification. Patients were analyzed based upon the presence or absence of TRFs, as determined in the initial prospective study.

Results: Data were available for 23 CIDP patients with a mean follow-up period of 44.7 mo. There were no differences in baseline or follow-up strength, disability, or IVIG usage in patients with a low number of fluctuations compared to those with a high number of fluctuations. In both groups, drug-free remission was achieved in about one-third of patients.

Discussion: TRFs are important to identify in order to optimize treatment in real time, but poorly predict long-term disease activity status. The presence of minor TRFs are unlikely to result in substantial accumulation of disability over time. Periodic IVIG optimization trials using objective outcomes are encouraged in all CIDP patients receiving chronic IVIG treatment as a means to identify the lowest effective IVIG dose and frequency.

KEYWORDS
CIDP, grip strength, immunoglobulin, outcome measures, treatment related fluctuations

List of Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; I-RODS, Inflammatory Rasch-built Overall Disability Scale; IVIG, intravenous immunoglobulin; MCID, minimal clinically important difference; MRC, Medical Research Council; TRFs, treatment-related fluctuations.

1 | INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired immune-mediated disorder with a heterogeneous clinical course. Approximately 30% of patients can achieve a durable period of drug-free remission at some point in their disease.[1] There are no known disease activity biomarkers that predict what dose, frequency, or duration of immunotherapy is needed, or if immunotherapy is needed at all. The process of determining disease activity entails weaning or suspending immunotherapy and monitoring for objective changes in clinical outcomes. The presence of objective deterioration following immunotherapy withdrawal suggests (but does not prove) that the disease is active and continued immunotherapy is appropriate. This paradigm, while far from perfect, is an important part of CIDP standard of care.[2]

The GRIPPER study attempted to understand disease activity by prospectively recording daily grip strength and weekly disability outcomes in patients with CIDP that were being treated with intravenous immunoglobulin (IVIG).[3] Intra-IVIG-cycle changes in grip strength relative to the pre-IVIG baseline were calculated and correlated with disability. A grip strength fluctuation was defined as ≥10% change on ≥2 consecutive 3-day averaged calculations. Less than this was deemed not clinically meaningful and thought to be due to day-to-day variation. Of 25 patients included in the study, 48% were found to have no or minimal grip strength fluctuations in between IVIG infusions, while 52% had substantial fluctuations. The study concluded that intra-IVIG-cycle grip strength fluctuations presumably reflect a difficult to measure underlying biologic process, and that by quantifying these fluctuations, IVIG optimization can be more precisely achieved.

While grip strength is a reliable and valid way to guide immunotherapy optimization in real time, the implications of treatment-related fluctuations (TRFs) for long-term CIDP prognosis or clinical impairment are unknown. The aim of this study was to determine if TRFs (1) predict the ability to achieve drug-free remission, (2) give insight into IVIG or other immunotherapy utilization patterns over time, or (3) portend deteriorations in strength and disability.

2 | METHODS

2.1 | Study design

This retrospective observational cohort study reviewed data from patients who participated in a published prospective study of intra-IVIG-cycle grip strength quantification. Identification of patients, methods used to determine treatment fluctuation classification (low/no vs. high), and ethics approvals are published elsewhere.[3]

2.2 | Study outcomes

For each participant, the date of GRIPPER study completion served as the study baseline. Medical records were reviewed for strength impairment [grip strength, Medical Research Council (MRC) scores], disability [Inflammatory Rasch-built Overall Disability Scale (I-RODS)], IVIG dose and frequency, use of additional immunotherapy, and disease activity status[1] during standard of care follow-up. All treatment decisions were at the discretion of the treating physician. IVIG taper trials were of particular interest. If IVIG was reduced (dose reduction or interval lengthening) and relapse occurred with the first change, then the taper was considered "not successful". If IVIG reductions were achievable below baseline but complete weaning was not possible, the taper was considered "partially successful". If IVIG was discontinued without the use of additional immunotherapy for at least 3 mo, then tapering was considered "completely successful." Three months was chosen as the threshold for "completely successful" based on prior studies that observed that most relapses following IVIG discontinuation occur within this time period.[4–6] Because this was a retrospective study that analyzed treatment behavior during routine clinical care, the precise definition of relapse (and, by extension, rationale for immunotherapy utilization) in any given patient could not be determined. Longitudinal changes in grip strength were considered stable if <10% different than baseline (using 3-day averaged recordings), MRC sum (60-point scale) if <2 points from baseline, and I-RODS if <4 points (centile scale) from baseline. Changes in grip strength, MRC sum score, and I-RODS outside of these boundaries were considered better or worse relative to baseline depending on the direction of change.

2.3 | Statistical analysis

Descriptive statistics including counts and percentages were used for nominal or dichotomous variables. Categorical variables were analyzed using the Pearson chi-squared and Fisher exact test. Statistical analysis was performed using Graphpad Prism 8 (San Diego, CA).

3 | RESULTS

Data were available for 23 of 25 patients who participated in the original study. After a mean follow-up of 44.7 mo, there were no differences in baseline or follow-up strength or disability scores in patients with a low number of fluctuations compared to those with a high number of fluctuations (Table 1). In both groups, drug-free remission was achieved in about one-third of patients. The frequency with which deterioration in grip strength, MRC sum score or I-RODS exceeded the minimal clinically important difference (MCID) for each measure and frequency of a sub-MCID deterioration is shown in Table 2. In the low fluctuaters, there was infrequent worsening of any outcome at last follow-up.

A total of six patients received a second immunotherapy (three from each group). Prior to initiation of another immunotherapy, there were no differences in the likelihood of partial or complete IVIG tapering success between groups, or with dose or frequency of IVIG

TABLE 1 Outcome measures at study baseline (end of GRIPPER study[3]) and last available clinical follow-up

		High fluctuaters (n = 12)	Low fluctuaters (n = 11)	p
Follow-up duration, mean (range), mo		45.8 (12–68)	43.6 (18–65)	0.78
Grip strength right, mean (range), kg	Baseline	26.1	30.0	0.63
	At last follow-up	28.1	32.8	0.46
Grip strength left, mean (range), kg	Baseline	24.3	27.5	0.69
	At last follow-up (n = 8)	27.0	33.2	0.36
MRC sum score (0–60), mean	Baseline	57.3	57.7	0.76
	At last follow-up	58.3	57.7	0.66
MRC FDI sum (0–10), mean	Baseline	8.1	8.7	0.29
	At last follow-up	8.7	8.6	0.96
I-RODS score, mean (range)	Baseline	70	69	0.96
	At last follow-up (n = 4)	76	79	0.81

Abbreviations: I-RODS, inflammatory Rasch-built Overall Disability Scale; MRC, Medical Research Council.

TABLE 2 Magnitude of strength impairment and disability change during clinical follow-up

	Deterioration definition	High fluctuaters	Low fluctuaters	p
Grip strength right	MCID (≥10%)	13% (1 of 8)	16% (1 of 6)	1.00
	Sub MCID	50% (4 of 8)	33% (2 of 6)	0.62
Grip strength left	MCID (≥10%)	13% (1 of 8)	0% (0 of 6)	1.00
	Sub MCID	38% (3 of 8)	16% (1 of 6)	0.58
MRC sum (0–60)	MCID (≥ 2 points)	8% (1 of 12)	9% (1 of 11)	1.00
	Sub MCID	17% (2 of 12)	18% (2 of 11)	1.00
I-RODS	MCID (≥ 4 points)	25% (2 of 8)	0% (0 of 4)	0.51
	Sub MCID	25% (2 of 8)	0% (0 of 4)	0.51

Abbreviations: I-RODS, Inflammatory Rasch-built Overall Disability Scale; MCID, minimal clinically important change; MRC, Medical Research Council.

TABLE 3 Changes in IVIG over time in patients with frequent fluctuations and patients with no or minimal fluctuations

		High fluctuaters (n = 12)	Low fluctuaters (n = 11)	p
IVIG taper attempted, % (n)		92% (11 of 12)	82% (9 of 11)	1.00
IVIG taper not successful, % (n)		45% (5 of 11)	44% (4 of 9)	1.00
IVIG taper partially successful, % (n)		18% (2 of 11)	22% (2 of 9)	1.00
IVIG taper completely successful, % (n)		36% (4 of 11)	33% (3 of 9)	1.00
IVIG dose, mean (gm/kg)	Baseline	0.91	0.89	0.76
	At last follow-up	0.75	0.77	0.89
IVIG frequency, mean (wk)	Baseline	4.2	3.6	0.40
	At last follow-up	3.1	3.9	0.42
IVIG per 4 wk, mean (g/kg)	Baseline	1.1	1.0	0.77
	At last follow-up	1.1	0.8	0.47

Abbreviation: IVIG, intravenous immunoglobulin.

administration during follow-up (Table 3). In the high fluctuating group, the second immunotherapy in all three patients was rituximab, with one patient not attempting IVIG tapering and two classified as "not successful." Two of these patients were subsequently found to harbor neurofascin 155 antibodies and were successfully tapered off IVIG only after rituximab administration. In the low fluctuating group, all three patients failed IVIG tapering. One was treated with rituximab and had an unchanged IVIG requirement during follow-up. The remaining two patients were successfully weaned off IVIG after a second immunotherapy was added. One patient received high dose cyclophosphamide and rituximab, and the other enrolled in a clinical trial.

4 | DISCUSSION

Similar to other studies, one-third of our CIDP patients achieved a durable period of drug-free remission.[1] We anticipated that patients would be more likely to reach this status if IVIG TRFs were low or absent. This finding was not observed. The presence or absence of IVIG TRFs did not predict long-term disease activity status or IVIG requirements over time. Our findings indicate that, when IVIG dose and frequency are optimized to individual patients, it may obviate intra-cycle clinical fluctuations, but this cannot be presumed to reflect an attenuation of the underlying immunobiology that determines disease activity status.

CIDP treatment guidelines highlight the importance of periodic IVIG taper trials during standard of care to determine the need for ongoing therapy and to find the lowest effective IVIG dose.[7]

We have previously demonstrated that grip strength is able to identify real-time TRFs, and that when these data are interpreted in the context of clinical changes, it provides an objective framework by which IVIG can be optimized to individual patient requirements.[3] We now also show that modest TRFs are usually tolerated without clinically meaningful long-term detrimental impact.

Our conclusions should be framed with an important caveat. TRFs in our patients, if present, were generally mild. Our findings cannot exclude the possibility that end-of-cycle deteriorations that result in substantial clinical impairment will lead to accumulation in disability over time. Instead, our findings (together with CIDP treatment guidelines[7]) suggest an approach to management that balances optimization of treatment to achieve a state of minimal expression of manifestations with tolerance to some TRFs. We advocate for evidence-based approaches to IVIG initiation[5] with utilization of objective outcomes of strength impairment and disability to demonstrate treatment response.[6] We further advocate for these outcomes to be used to optimize IVIG dose and frequency to the specific needs of an individual patient.[3] If fluctuations are absent or minimal, we demonstrate herein that there is likely minimal risk for accumulation of clinical impairment over time. If fluctuations result in clinically meaningful end of cycle worsening, then treatment parameters may be adjusted such that real-time fluctuations and the theoretical risk of accumulating impairment is minimized.

Our study has several important limitations. First, the small number of patients and sometimes incomplete datasets made statistical differences challenging to detect. Second, while deteriorations greater than MCID were infrequent, in some patients changes less than MCID may still be clinically meaningful and are not reflected in the arbitrary cutoff values of this study's TRF definition.[8] In clinical practice, any change in outcome should be taken on a case-by-case basis to determine the importance. Third, longer follow-up is needed to fully understand the risk and magnitude of accumulating strength impairment and disability, especially when minor TRFs are present over extended periods of time. Finally, this study does not adequately account for sensory disturbances.

Our findings demonstrate that TRFs, while important to optimize real-time treatment, poorly predict long-term disease activity. Minor TRFs are unlikely to result in substantial accumulation of disability over time. These findings provide reassurance that emergence of modest end-of-cycle symptoms during IVIG treatment may not always necessitate escalation in IVIG dose or infusion frequency.

AUTHOR CONTRIBUTIONS

Mamatha Pasnoor: Data curation; investigation; writing – review and editing. **Senda Ajroud-Driss:** Data curation; investigation; writing – review and editing. **Thomas H. Brannagan:** Data curation; investigation; writing – original draft; writing – review and editing. **Mazen M. Dimachkie:** Data curation; investigation; writing – original draft; writing – review and editing.

ACKNOWLEDGEMENTS

This study was funded by an investigator-initiated grant provided by CSL Behring. The authors thank CSL Behring for their support.

FUNDING INFORMATION

Funding provided by CSL Behring in the form of an investigator-initiated grant.

CONFLICTS OF INTEREST

Melissa Cook: None. Mamatha Pasnoor: Has provided consulting services to TerumboCT, Alexion, CSL Behring, Argenx, Momenta, Catalalyst. Senda Ajroud-Driss: Has provided consulting services to Alnylam Pharmaceutical, Akcea therapeutics, MT pharma, Biohaven and Biogen. Thomas Brannagan: Has provided consulting services to Akcea, Alnylam, Argenx, CSL-Behring, Grifols, Ionis, Takeda and Pfizer and has research support from Alnylam, Argenx, Grifols, Pharnext, Ionis, and UCB Biopharma. Mazen M Dimachkie: Has provided consulting services to Amazentis, ArgenX, Catalyst, Cello, Covance/Labcorp, CSL-Behring, EcoR1, Janssen, Kezar, Medlink, Momenta, NuFactor, Octapharma, RaPharma/UCB, Roivant Sciences Inc, Sanofi Genzyme, Shire Takeda, Scholar Rock, Spark Therapeutics, Abata/Third Rock, UCB Biopharma and UpToDate. Dr. Dimachkie received research grants or contracts or educational grants from Alexion, Alnylam Pharmaceuticals, Amicus, Biomarin, Bristol-Myers Squibb, Catalyst, Corbus, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Kezar, Mitsubishi Tanabe Pharma, MDA, NIH, Novartis, Octapharma, Orphazyme, Ra Pharma/UCB, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, The Myositis Association, UCB Biopharma / RaPharma, Viromed/Healixmith & TMA. Jeffrey A Allen: Has provided consulting services to Akcea, Alexion, Argenx, Momenta, Grifols, Johnson & Johnson, Octapharma, CSL Behring, Biotest, Takeda.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Melissa Cook https://orcid.org/0000-0002-2791-4342
Jeffrey A. Allen https://orcid.org/0000-0001-8753-2680

REFERENCES

1. Gorson KC, Van Schaik IN, Merkies IS, et al. Chronic inflammatory demyelinating polyneuropathy disease activity status: recommendations for clinical research standards and use in clinical practice. *J Peripher Nerv Syst*. 2010;15(4):326-333.
2. Allen JA, Berger M, Querol L, Kuitwaard K, Hadden RD. Individualized immunoglobulin therapy in chronic immune-mediated peripheral neuropathies. *J Peripher Nerv Syst*. 2018;23(2):78-87.
3. Allen JA, Pasnoor M, Dimachkie M, et al. Quantifying treatment-related fluctuations in CIDP: results of the GRIPPER study. *Neurology*. 2021;96(14):e1876-e1886.
4. Vanhoutte EK, Latov N, Deng C, et al. Vigorimeter grip strength in CIDP: a responsive tool that rapidly measures the effect of IVIG–the ICE study. *Eur J Neurol*. 2013;20(5):748-755.
5. 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 randomized placebo-controlled trial. *Lancet Neurol*. 2008;7(2):136-144.
6. Allen JA, Merkies IS, Lewis RA. Monitoring clinical course and treatment response in chronic inflammatory demyelinating polyneuropathy during routine care: a review of clinical and laboratory assessment measures. *JAMA Neurol*. 2020;77(9):1159-1166.
7. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European academy of neurology/ peripheral nerve society. European Federation of Neurological Societies/peripheral nerve society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task-second revision. *J Peripher Nerv Syst*. 2021;26(3):242-268.
8. Keh RYS, Selby DA, Jones S, et al. Predicting long-term trends in inflammatory neuropathy outcome measures using latent class modelling. *J Peripher Nerv Syst*. 2022;27(1):84-93.

How to cite this article: Cook M, Pasnoor M, Ajroud-Driss S, Brannagan TH, Dimachkie MM, Allen JA. CIDP prognosis in patients with IVIG treatment-related fluctuations. *Muscle & Nerve*. 2023;67(1):69-73. doi:10.1002/mus.27746

Autophagy in non–immune-mediated rhabdomyolysis: Assessment of p62 immunohistochemistry

Ignacio Javier Acosta MD [1,2,3,4] | **Werner Stenzel MD** [5] | **Monika Hofer MBChB, FRCPath** [1] | **Stefen Brady DPhil, FRCP** [6]

[1]Neuropathology Department, John Radcliffe Hospital, Oxford University Hospitals Trust, Oxford, UK

[2]Translational Neurology and Neurophysiology Laboratory, Advance Clinical Research Centre, School of Medicine, Universidad de Chile, Santiago, Chile

[3]Neurology and Psychiatry Department, Clínica Alemana, Santiago, Chile

[4]Neurology and Neurosurgery Department, Clínica Dávila, Santiago, Chile

[5]Department of Neuropathology, Charité-Universitätsmedizin Berlin, Berlin, Germany

[6]Oxford Muscle Service, Department of Neurology, John Radcliffe Hospital, Oxford University Hospitals Trust, Oxford, UK

Correspondence
Ignacio Javier Acosta, Neurology and Psychiatry Department, Clínica Alemana, Vitacura 5951, Santiago, Chile.
Email: ignacioacosta@uchile.cl

Abstract

Introduction/Aims: p62 immunochemistry (IHC) has been shown to aid diagnosis with distinct patterns of muscle fiber staining observed in some inflammatory, hereditary, and degenerative myopathies, such as immune-mediated necrotizing myopathy (IMNM). The pattern of p62 staining may help narrow the pathological differential diagnosis of rhabdomyolysis. However, there is a lack of information on the pattern of p62 IHC in non–immune-mediated rhabdomyolysis. In this study we aim to describe histopathological findings in non–immune-mediated rhabdomyolysis, with particular emphasis on the pattern of p62 IHC.

Methods: We retrospectively reviewed the histopathological features of patients with a confirmed diagnoses of non–immune-mediated rhabdomyolysis referred to our center.

Results: Five patients were identified. Rhabdomyolysis was determined to be due to statin-associated toxicity in three patients, alcohol overuse in one patient, and intensive exercise in one patient. All patients showed increased numbers of necrotic and

Abbreviations: CK, creatine kinase; FoxO, factor Forkhead box O; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; IBM, inclusion-body myositis; IHC, immunochemistry; IMNM, immune-mediated necrotizing myopathy; LC3BII/LC3BI, protein 1 light-chain 3 beta II and I; MHC, Major Histocompatibility Complex; p62, sequestosome-1; PAS, periodic acid-Schiff; SDH, succinate dehydrogenase.

Monika Hofer and Stefen Brady contributed equally to this study.