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Clinical-neurophysiological correlations in chronic inflammatory demyelinating polyradiculoneuropathy patients treated with subcutaneous immunoglobulin

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Abstract

Introduction: Despite the well-described clinical efficacy of long-term subcutaneous immunoglobulin (LT-SCIg) in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) patients, the neurophysiological effects of SCIg have been followed only for a short time and were not correlated with clinical parameters.

Methods: Fourteen CIDP patients were evaluated at baseline and after LT-SCIg administration for 24 to 48 months. Nerve conduction studies were performed and clinical features were assessed for: (a) overall strength, by Medical Research Council sum score; (b) sensory function, by Inflammatory Neuropathy Cause And Treatment score; (c) disability, by Rasch-built overall disability scale; (d) quality of life (QoL), by the EuroQol Visual Analog Scale.

Results: LT-SCIg treatment improved clinical and neurophysiological features, preserving strength and improving sensory deficits, disability, and QoL. Clinical scores correlated with the amplitude of distal motor action (dCMAP) and sensory nerve action (SNAP) potentials.

Discussion: LT-SCIg treatment demonstrates efficacy in maintaining and continuing clinical improvement at 24 to 48 months after start of treatment. dCMAP and SNAP amplitudes represent useful prognostic factors for functional outcome.

KEYWORDS

CIDP, dCMAP, INCAT, MRCS score, nerve conduction, quality of life, R-ODS, SNAP, subcutaneous immunoglobulin

1 | INTRODUCTION

Long-term subcutaneous immunoglobulin (LT-SCIg) is a safe, effective, and tolerable alternative therapy in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).[1] The lower profile of side effects when compared with intravenous immunoglobulin (IVIg) and its comparable clinical efficacy,[2,3] together with lower direct

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; dCMAP, distal compound muscle action potential; DML, distal motor latency; EQ-VAS, EuroQol Visual Analog Scale; ICC, intraclass correlation coefficient; INCAT, Inflammatory Neuropathy Care And Treatment; LL, lower limb; MCV, motor conduction velocity; MRC, Medical Research Council; NCS, nerve conduction studies; pCMAP, proximal compound muscle action potential; QoL, quality of life; R-ODS, Rasch-built Overall Disability Scale; SCIg, subcutaneous immunoglobulin; SCV, sensory conduction velocity; SNAP, sensory nerve action potential; UL, upper limb.

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(drugs for premedication, health-care professional time) and indirect costs (eg, loss of working time for the patient/caregiver, transport),[4] make this treatment widely accepted and well tolerated,[5-7] even for long-term treatment. The large PATH trial in CIDP patients demonstrated that LT-SCIg for 24 weeks can be used as a maintenance treatment in patients with CIDP.[8,9] Moreover, SCIg diminishes the fluctuations in physical performance, with preservation of overall strength and disability and significant improvement in quality of life (QoL).[10] Recently, two neurophysiological parameters, amplitude of distal compound muscle action potential (dCMAP) and sensory nerve action potential (SNAP), correlated significantly with clinical parameters in CIDP patients treated with SCIg for 24 months, highlighting the importance of neurophysiological follow-up.[11] The importance of neurophysiological monitoring has been highlighted by the addition of the dCMAP duration to the diagnostic criteria for CIDP,[12,13] and represents a sensitive and specific marker of CIDP.[14,15] The progressive increase in dCMAP amplitude after SCIg treatment,[11] together with the reduced dCMAP duration, may be related to the resolution of nerve focal/diffuse demyelination (eg, conduction blocks, temporal dispersion) but also to the SCIg-induced axonal regeneration/reinnervation and/or reduced axonal loss.

Although the efficacy of SCIg with regard to clinical features has been thoroughly evaluated,[9,10] the neurophysiological effects of SCIg in CIDP patients have been followed only for a short time,[16] and the putative correlations between neurophysiological features and clinical parameters (strength, sensory scores, disability, QoL) have not yet been investigated. Therefore, in this study we aimed to evaluate the effects of LT-SCIg treatment on nerve conduction parameters, clinical features, and QoL in CIDP patients.

2 | METHODS

2.1 | Patient population and treatment

This prospective study included 14 patients (8 males and 6 females) affected by typical and definite CIDP[13] and treated with SCIg for 48 months at the I Division of Neurology and Neurophysiopathology of the University of Campania "Luigi Vanvitelli," between the years 2016 and 2018.

At the time of the diagnosis (2014), 20 CIDP patients (12 males and 8 females) were treated with one infusion of IVIg per day for 5 days (Privigen; CSL Behring) at a dose of 0.4 g/kg/day. Four weeks after the last IVIg infusion, IVIg responders (n = 16, 9 males and 7 females) were shifted to the SCIg treatment (Hizentra 20%; CSL Behring), consisting of two subcutaneous infusions per week (0.4 g/kg/week), followed by clinical and neurophysiological evaluation at 24 and 48 months. We excluded two patients with interrupted SCIg treatment after 24 months due to clinical remission. All patients with concurrent treatments (steroids, plasmapheresis, immunosuppressants) were excluded. The SCIg treatment for CIDP patients is included in the standard care protocol of the University of Campania "Luigi Vanvitelli." All participants provided written informed consent with the protocol approved by the local ethics committee.

2.2 | Clinical parameters

CIDP patients were clinically evaluated using established assessment scales and scores at baseline (before SCIg treatment) and after 24 and 48 months of SCIg treatment. Strength was evaluated using the modified Medical Research Council sum (MRCS) score, a summation of the MRC grades (0-5) of the following muscle pairs: shoulder abductors, elbow flexors, wrist extensors, knee extensors, and ankle dorsiflexors.[17] The MRCS score, therefore, ranged from 0 (complete paralysis) to 60 (normal strength). For sensory evaluation, we used the Inflammatory Neuropathy Cause And Treatment (INCAT) sensory sum score,[18,19] a multimodality sensory scale ranging from 0 (normal sensation) to 20 (severe sensory deficit). The Rasch-built Overall Disability Scale (R-ODS) for immune-mediated neuropathies[20] is a 24-item scale for daily activity and social participation limitations, ranging from 0 (not possible to perform) to 48 (possible without any difficulty), and was used to assess disability. QoL was evaluated with the EuroQoL Visual Analog Scale (EQ-VAS) of the EQ-5D-5L questionnaire,[21] recording the respondent's self-rated health on a scale ranging from "best health" (score = 100) to "worst health" (score = 0).

2.3 | Nerve conduction studies

Nerve conduction parameters (NCPs) were assessed at baseline (before SCIg treatment) and after treatment with SCIg for 24 and 48 months, using a Synergy electromyography machine (Synopo, Milan, Italy), according to the guidelines of the American Association of Neuromuscular & Electrodiagnostic Medicine.[22] As previously reported,[11] we assessed motor nerve conduction, recording the distal motor latency (DML), dCMAP and pCMAP amplitudes, and motor conduction velocity (MCV) from the median, ulnar, peroneal, and tibial nerves, bilaterally.

For sensory conduction, we recorded SNAP amplitude and sensory conduction velocity (SCV) from radial (forearm–I metacarpal bone), median (wrist–digit III), ulnar (wrist–digit V), superficial peroneal (leg–ankle), and sural (sural region–lateral malleolus) nerves, bilaterally.

2.4 | Statistical analysis

Mean dCMAP and pCMAP amplitude, DML, MCV, SCV, and SNAP amplitudes were evaluated after SCIg treatment for 24 and 48 months for the upper limbs (ULs) and lower limbs (LLs). One-way analysis of variance was used for quantitative data. Correlations of NCPs and clinical data (MRCS, INCAT, R-ODS, and EQ-VAS scores) were performed at baseline and 24 months and 48 months after treatment, using regression linear analysis (Pearson r value). Test–retest reproducibility for intraindividual variation (examiner V.T.) was assessed using the intraclass correlation coefficient (ICC) value ≥0.75 for excellent reliability.[23] Data were analyzed using SigmaPlot version 10.0 software and expressed as mean ± standard deviation (SD), with $P \leq .05$ considered significant, using the Bonferroni method for multiple comparisons.

3 | RESULTS

3.1 | Clinical evaluation and correlations

Table 1 shows the demographic data of the CIDP patients. Clinical data at baseline and after LT-SCIg treatment are presented in Table 2. The MRCS score increased progressively after SCIg treatment for 24 and 48 months, as compared with the basal value (Figure 1). The increase in MRCS score was significant when comparing the baseline value with the score at 24 months, highlighting the efficacy of SCIg treatment on strength recovery; however, no significant difference was found between MRCS score at 24 and 48 months, suggesting that LT-SCIg treatment was also effective in strength preservation over time.

The INCAT, R-ODS, and EQ-VAS scores progressively improved after treatment with SCIg for 48 months, compared with the values at 24 months and before SCIg treatment (Figure 1).

Altogether, these data highlight the efficacy of LT-SCIg treatment in strength preservation and sensory function, reducing disability and improving QoL.

TABLE 1 Demographic data

Parameters	CIDP patients (n = 14)
Age (years)[a]	63.6 ± 12.8
Gender (males/females)	8/6
Disease duration (years)[a]	1.3 ± 0.8
Duration of SCIg treatment (months)[a]	49.8 ± 1.3
Infusion duration (hours)	1.5
SCIg dose (g/Kg/week)	0.4
Range of SCIg dose (g/week)	30.0-35.0
Mean SCIg dose (g/week)[a]	31.4 ± 2.3

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; SCIg, subcutaneous immunoglobulin.
[a]Data expressed as mean ± standard deviation.

3.2 | Neurophysiological parameters

Table 3 summarizes neurophysiological features at baseline and after SCIGg treatment for 24 and 48 months for ULs and LLs. For the motor nerve conduction, the mean DML was progressively reduced after 48 months of treatment with SCIg compared with 24 months and baseline. In contrast, the mean dCMAP and pCMAP amplitudes and MCVs were significantly increased after SCIg treatment for

TABLE 2 Clinical data[a]

Clinical scores/cut-off	Baseline	24 months	P^b	48 months	P^c
MRCS/60	30.3 ± 7.0	56.5 ± 2.5	**.00037***	58.1 ± 1.4	.442
INCAT/20	17.5 ± 3.2	12.9 ± 2.3	**.031***	8.0 ± 2.8	**.00054***
R-ODS/48	28.8 ± 5.2	36.5 ± 3.9	**.027***	45.5 ± 3.0	**.00039***
EQ-VAS/100	51.5 ± 8.1	69.4 ± 8.4	**.016***	86.0 ± 7.5	**.00031***

Abbreviations: EQ-VAS, EuroQol Visual Analog Scale score; INCAT, Inflammatory Neuropathy Cause And Treatment; MRCS, Medical Research Council sum score; R-ODS, Rasch-built Overall Disability Scale score.
[a]Data expressed as mean ± standard deviation, corrected for multiple comparisons.
[b]Baseline vs 24 months.
[c]24 months vs 48 months.
*Statistically significant ($P < .05$).

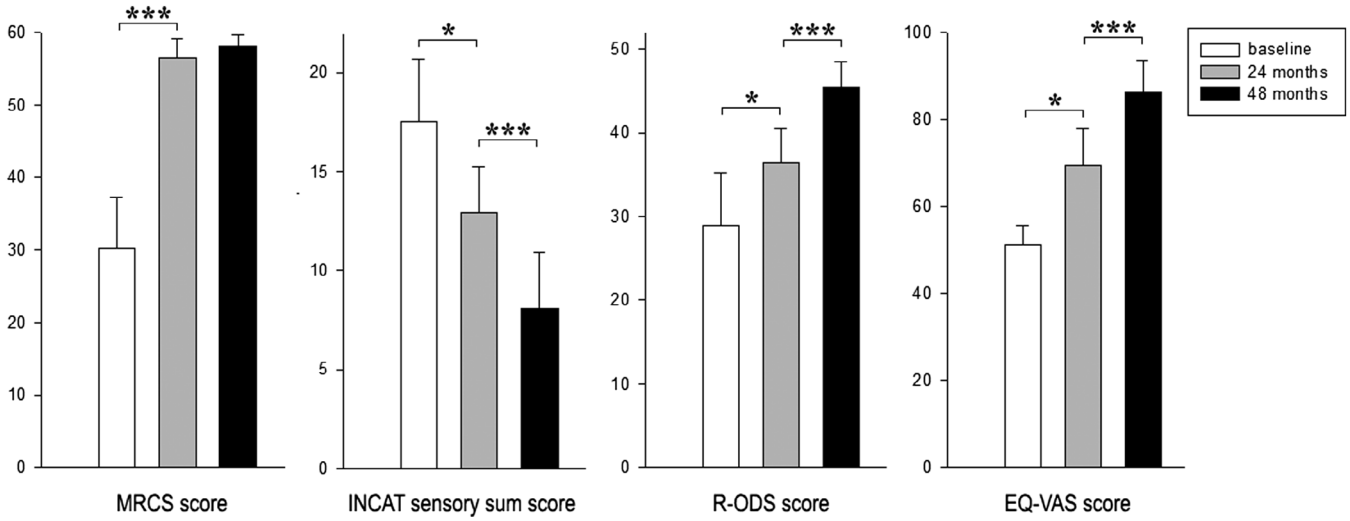

FIGURE 1 Clinical parameters (mean MRCS, INCAT sensory, R-ODS, and EQ-VAS scores) at baseline and after SCIg treatment for 24 and 48 months. Data are presented as mean ± standard deviation (*$P \leq .05$; ***$P \leq .0001$). EQ-VAS, EuroQol Visual Analog Scale; INCAT, Inflammatory Neuropathy Cause And Treatment; R-ODS score, Rasch-built Overall Disability Scale score; MRCS score, Medical Research Council sum score; SCIg, subcutaneous immunoglobulin

TABLE 3 Neurophysiological findings[a]

		Upper limbs				Lower limbs			
Parameter	ICC	t_0	24 months	48 months	*P*	t_0	24 months	48 months	*P*
DML (ms)	0.97	8.0 ± 2.7	4.6 ± 2.9	3.8 ± 1.2	**.038***	8.2 ± 2.3	6.2 ± 1.9	5.1 ± 1.9	**.015***
pCMAP (mV)	0.90	2.1 ± 1.4	6.6 ± 1.6	8.6 ± 3.8	**.017***	1.9 ± 1.1	3.5 ± 1.6	5.6 ± 4.3	**.013***
dCMAP (mV)	0.98	4.9 ± 1.9	8.9 ± 2.7	11.5 ± 3.4	**.026***	2.7 ± 0.8	5.1 ± 1.4	7.0 ± 5.0	**.007***
MCV (m/s)	0.87	34.5 ± 8.4	39.5 ± 10.6	48.4 ± 11.2	**.013***	28.3 ± 5.7	29.7 ± 9.6	35.8 ± 10.6	**.00024***
SNAP (μV)	0.98	1.8 ± 0.4	4.7 ± 0.6	11.5 ± 8.1	**.00057***	1.3 ± 0.7	3.6 ± 0.9	6.1 ± 4.6	**.00011***
SCV (m/s)	0.95	31.4 ± 4.3	32.4 ± 8.4	43.9 ± 7.7	**.00043***	29.5 ± 3.7	30.5 ± 6.4	36.9 ± 7.5	**.00031***

Abbreviations: DML, distal motor latency; ICC, intraclass correlation coefficient; MCV, motor conduction velocity; ms, milliseconds; mV, milliVolt; μV, microVolt; m/s, meter for second; pCMAP-dCMAP, proximal-distal compound motor action potential; SCV, sensory conduction velocity; SNAP, sensory nerve action potential.
[a]Data expressed as mean ± standard deviation, corrected for multiple comparisons analysis of variance.
*$P < .05$ (statistically significant).

TABLE 4 Clinical-neurophysiological correlations (Pearson linear correlation)[a]

	Upper limbs				Lower limbs			
Parameter	MRCS	INCAT	R-ODS	EQ-VAS	MRCS	INCAT	R-ODS	EQ-VAS
dCMAP (mV)	0.81 (0.67-0.92)	—	0.72 (0.67-0.84)	0.68 (0.58-0.81)	0.72 (0.67-0.84)	—	0.62 (0.52-0.73)	0.65 (0.58-0.79)
SNAP (μV)	—	−0.58 (0.47-0.72)	0.68 (0.48-0.76)	0.65 (0.57-0.75)	—	−0.57 (0.47-0.66)	0.71 (0.61-0.82)	0.71 (0.67-0.86)

Abbreviations: dCMAP, distal compound motor action potential; EQ-VAS, EuroQol Visual Analog Scale; INCAT, Inflammatory Neuropathy Cause and Treatment; MRCS, Medical Research Council sum; mV, milliVolt; μV, microVolt; R-ODS, Rasch-built Overall Disability Scale; SNAP, sensory nerve action potential.
[a]Data expressed as *R* value (confidence interval). $P \leq .001$ for all correlations.

48 months when compared with 24-month and baseline values. For sensory nerve conduction, the mean SNAP amplitude and SCV were significantly increased after SCIg treatment for 48 months compared with 24-month and baseline values. We did not detect any changes in CMAP morphology, temporal dispersion, or conduction block.

3.3 | Clinical-neurophysiological correlation analysis

Table 4 shows the results of linear regression analysis, used to correlate NCPs with clinical scores after SCIg treatment at 24 and 48 months.

dCMAP amplitude positively correlated with MRCS, R-ODS, and EQ-VAS scores (Figure S1 online), suggesting that dCMAP amplitude correlated with strength recovery and preservation, while also reflecting the reduced disability and improved QoL after LT-SCIg treatment.

SNAP amplitude correlated negatively with the INCAT sensory score and positively with R-ODS and EQ-VAS (Figure S2 online), highlighting the impact of sensory symptoms/deficits on disability and QoL.

4 | DISCUSSION

Our study findings suggest that LT-SCIg treatment in CIDP patients leads to improvement and preservation of overall strength, sensory deficits, disability, and QoL, paralleled by progressive improvement of NCPs. We also found significant correlations between the amplitude of dCMAP and SNAP and the MRCS, INCAT, R-ODS, and EQ-VAS scores at baseline and after SCIg therapy, conferring prognostic value to the dCMAP and SNAP amplitudes and highlighting the importance of neurophysiological monitoring during SCIg treatment.

A number of studies supported the LT-SCIg as the "gold standard" treatment for immune-mediated polyneuropathies,[24] with improvement of QoL[4,6,7] and strength in almost all CIDP patients.[17,25] Results from the PATH study,[8] the first large, randomized trial with two SCIg doses in CIDP, indicate that SCIg treatment, using a weekly dose of 0.2 to 0.4 g/kg, is efficacious and well tolerated in the maintenance of Ig-responsive CIDP patients and in preventing relapse,[26] with considerable implications for the cost of treatment and QoL.[9,27,28]

SCIg treatment for 24 months significantly improved motor strength and MRCS score compared with baseline and was effective in strength preservation until 48 months (Figure 1). Therefore, an extended clinical follow-up is mandatory to verify whether MRCS score stability between 24 and 48 months may be the expression of an intrinsic limitation of the scale, which may not be sensitive enough to detect subtle improvements in strength, particularly for distal limb muscles.

Typical CIDP is a length-dependent polyneuropathy, characterized by distal clinical presentation, first affecting the lower then the upper extremities.[29,30] Therefore, we evaluated neurophysiological parameters at ULs and LLs, showing significant improvement of all NCPs after SCIg treatment. In particular, dCMAP amplitude significantly increased at 48 months compared with 24 months and baseline, suggesting that LT-SCIg treatment may be involved in the resolution of demyelinating/remyelinating features

of nerve conduction, including distal conduction blocks[31] and temporal dispersion, but also in promoting distal-to-proximal reinnervation and preventing secondary axonal degeneration.

Clinical-neurophysiological correlations demonstrated a positive and direct correlation of the dCMAP amplitude, with increased strength, reduced disability, and improved QoL. The SNAP amplitude showed a direct but inverse correlation with the INCAT sensory score (ie, greater SNAP amplitude is associated with reduction of sensory deficits) and a direct positive correlation with both R-ODS and EQ-VAS scores (ie, greater SNAP amplitude is associated with reduced disability and improved QoL). These correlations demonstrate that disability and QoL are dependent on dCMAP and SNAP amplitudes, underling the importance of monitoring NCPs in addition to periodic clinical observations to evaluate the long-term clinical outcome in CIDP patients.

Our study has some limitations. First, our patient population consisted exclusively of excellent responders to immunoglobulin treatment (first IVIg and then SCIg). We are aware of this bias, but the aim of the present study was to extend the data analysis of our previous work,[11] in which we analyzed the clinical and neurophysiological response at 12 and 24 months after SCIg treatment in CIDP patients. Second, a larger group of patients could have added significant details on LT-SCIg therapy; however, this was a homogeneous group of Ig-responder patients and ideal for analysis of both clinical and neurophysiological response to SCIg treatment. Third, despite the recent suggestion of a novel regimen of SCIg administration (bolus dose, a concentrated dose every week)[32] for CIDP maintenance therapy or the intermittent reduction of the weekly SCIg dose to test for remission,[33] our treatment was continued for 48 months without dose changes because we had previously observed persistent alterations of nerve conduction at 24 months,[11] but also progressive clinical improvement, reduced disability, and improved QoL.

Taken together, our results support LT-SCIg treatment in CIDP patients as it combines clinical efficacy, good functional outcome, reduced disability, and improved QoL. Evidence suggests that SCIg treatment should be started early after IVIg infusions, consisting of two infusions per week at a dose of 0.2 to 0.4 g/kg/week. Treatment duration should be based on clinical response and on neurophysiological monitoring. Herein we have shown that LT-SCIg treatment results in progressive improvement of NCS parameters, improving demyelinating features of nerve conduction (conduction blocks, conduction velocity), prompting us to also hypothesize a role in axonal regeneration and reduction of axonal loss. Therefore, despite the relevance of clinical scales for outcome evaluation, we have highlighted the importance of neurophysiological monitoring, in particular of dCMAP and SNAP amplitudes, as they represent useful prognostic factors for functional outcome and for estimating the necessary duration of SCIg treatment. Managing CIDP therapy over the long term is the key to treatment success.

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CONFLICTS OF INTEREST

The authors declare no potential conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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