Clinical Neurology and Neurosurgery 198 (2020) 106240

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Manual push technique, an alternative route of subcutaneous immunoglobulin administration in chronic inflammatory demyelinating polyradiculoneuropathy: A proof-of-concept study

Dario Cocito [a,*], Erdita Peci [a], Simona Rigaldo [b], Carlotta Canavese [b], Giuseppe Migliaretti [c], Federico M. Cossa [a]

[a] Divisione di Riabilitazione Neuromotoria, Istituti Clinici Scientifici Maugeri, Presidio Sanitario Major, Via Santa Giulia, 60, 10124, Torino, Italy
[b] Dipartimento di Neuroscienze – Università di Torino, A.O.U. Città della Salute e della Scienza di Torino, Corso Bramante, 88, 10126, Torino, Italy
[c] Dipartimento di Sanità Pubblica e Scienze Pediatriche – Università di Torino, Piazza Polonia, 94, 10126 Torino, Italy

ARTICLE INFO

Keywords:
Neuropathology
Randomized clinical trial
Demyelinating diseases
Polyradiculitis
Polyneuropathy
Chronic inflammatory demyelinating polyradiculoneuropathy

ABSTRACT

Objective: Subcutaneous immunoglobulin (SCIg) administered through infusion pump has been reported as effective in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) patients. In this study we evaluate an alternative technique of SCIg administration, based on the delivery of lower volumes administered daily using manual push technique (MPT) in 10 CIDP patients.
Methods: In this randomized, controlled, two-arm, crossover clinical trial, CIDP patients were randomly assigned 1:1 to receive SCIg either by MPT or pumps for 4 consecutive months with crossover to the other. The primary objective was to assess whether MPT had the same effectiveness as pumps. The secondary objectives were to assess whether MPT resulted in greater plasma IgG levels and improved quality of life (QoL).
Results: Ten patients (mean age = 48.3) were enrolled. No significant changes were observed in the efficacy parameters (INCAT, MRC, R-ODS, and GS scales). A positive mean variation of 5.4 % in plasma IgG levels in the group treated with MPT was observed at the end of MPT periods. Treatment interference, which is one of the dimensions of the Life Quality Index, showed a significant improvement in the MPT periods.
Conclusion: In CIDP patients, the MPT technique was as effective as pump infusion, allowed comparable, slightly increases plasma IgG levels, and also improved the QoL.

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired chronic peripheral sensory-motor neuropathy presenting with a progressive weakness in the limbs [1] with a prevalence ranging from 0.8 to 8.9/100,000. Over half (54 %) of CIDP patients have disabilities with a modified Rankin scale grade 4 or 5 [2]. CIDP is variably characterized by a progressive, relapsing-remitting or monophasic course involving everyday life activity and quality of life (QoL) of affected patients [1]. There is a general consensus that CIDP is an immune-mediated disorder. It is treated with immune therapies including steroids, plasma exchange, and high-dose intravenous immunoglobulin (IVIg) that are effective in 50–80 % of patients [3–7]. IVIg treatment needs to be continued for a long period of time to avoid patient relapse after therapy suspension.

Multicenter studies have demonstrated that CIDP treatment through subcutaneous immunoglobulin (SCIg) could be an effective alternative to IVIg [8–10].

SCIg may be administered using two techniques:

- Pump administering 50−100 ml per infusion: depending on the selected dose per kg, patients have to undergo 1–3 weekly administrations if the preparation has a 20 % concentration; or
- Manual push technique (MPT), involving self-administration (day or multi-day) of small doses of immunoglobulin.

To date, no studies on the use of MPT in CIDP patients have been published. Conversely, its use for primary immunodeficiency diseases

* Corresponding author at: Via Santa Giulia, 60, 10124, Torino, Italy.
E-mail addresses: dariococito@yahoo.it (D. Cocito), erditapeci@gmail.com (E. Peci), simonarigaldo@yahoo.com (S. Rigaldo), ccanavese@cittadellasalute.to.it (C. Canavese), giuseppe.migliaretti@unito.it (G. Migliaretti), federico.cossa@icsmaugeri.it (F.M. Cossa).

https://doi.org/10.1016/j.clineuro.2020.106240
Received 30 April 2020; Received in revised form 10 August 2020; Accepted 13 September 2020
Available online 16 September 2020

(PIDD) has been documented.

As shown by Shapiro [11] in his retrospective medical record review of data from 173 PIDD patients on IgG replacement therapy, MPT is a feasible, effective, convenient, and safe alternative to infusion pump. MPT decreases the duration of administration but requires more frequent infusions. Patients self-administering SCIg through this technique reported fewer adverse events than their counterparts on infusion pump (15.6 % vs. 20.7 %). This previous study suggested that a standard monthly IgG dose, administered more frequently at a lower volume per infusion, could reduce plasma IgG catabolism, and thus result in a higher serum IgG level [11].

This proof-of-concept study aims to evaluate the feasibility and (both clinical and laboratory) efficacy of a novel regimen of immunoglobulin administration involving daily administration of lower SCIg volumes using MPT in CIDP patients. We postulated that daily manual administration of SCIG through a syringe (maintaining the same cumulative monthly dose) might have comparable effectiveness to that of mono-triweekly administration performed using a pump.

Since immunoglobulins have linear pharmacokinetics (the greater the quantity injected, the greater the rate of its catabolism) [12], we assessed whether MPT could increase plasma IgG levels more than infusion pumps. We also evaluated whether it improved the QoL.

2. Methods

2.1. Patients

We performed polyneuropathy inflammatory manual push assessment (the "PIMPA" study), a randomized, controlled, two-arm, crossover interventional clinical trial.

Patients referring to Divisione di Riabilitazione Neuromotoria, Istituti Clinici Scientifici Maugeri (Torino) and Dipartimento di Neuroscienze, A.O.U. Città della Salute e della Scienza di Torino were recruited. Follow-ups occurred in the period 30/7/2018−1/6/2019.

Inclusion criteria included: definite or probable CIDP as defined by the EFNS/PNS criteria [13], availability of results for nerve conduction studies (NCS) performed within 12 months prior to the screening, previous sustained response to IVIg therapy with evidence of "wear-off" effect, administration of SCIg through infusion pump for 3 months prior to enrollment at the same monthly dose as the last IVIg infusion.

Exclusion criteria included any serious medical condition that could interfere with the clinical assessment or MPT feasibility and anticipated poor compliance of the patient or caregiver with study procedures. Ten patients were randomly assigned 1:1 to receive SCIg either by MPT (given as 2 g, i.e., 10 mL per daily infusion) or pumps for 4 consecutive months with crossover to the other. All patients received 60 g /month of SCIg (IgG 20 %).

All subjects gave written informed consent and we obtained ethical committee approval (CS2/833 Prot. n° 0078380, 27 July 2018) from Comitato Etico Interaziendale Città della Salute e della Scienza di Torino. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. Objectives and outcome measures

The primary objective and secondary objectives of the study were to assess whether MPT had the same effectiveness as pump administration and whether MPT resulted in greater plasma IgG levels and improved the QoL compared to pump administration, respectively.

The primary outcomes were the following clinical efficacy parameters, which were assessed monthly:

- Inflammatory neuropathy cause and treatment (INCAT) disability scale;
- Medical Research Council (MRC) scale, evaluating eight muscle groups bilaterally (shoulder abduction, elbow flexion, wrist extension, first dorsal interosseous, hip flexion, knee extension, and ankle flexion/extension) with a maximum score of 80 points;
- Rasch-built Overall Disability Scale (R-ODS);
- Grip strength (GS), as measured using the Martin vigorimeter.

The secondary outcomes were:

- Plasma IgG levels, assessed monthly just before the subsequent SCIg infusion;
- Life Quality Index (LQI), measured at the end of each treatment period. This is a validated scale assessing "treatment interference", "therapy-related problems," "therapy setting," and "treatment costs."

Finally, we also evaluated the number and type of SCIg-related adverse events during each study period.

2.3. Sample size

Based on the non-inferiority design of the study and considering a clinically relevant variation of 15 % with a non-inferiority of 10 % of the INCAT scale (one of the principal outcomes of the study), a sample size of 10 subjects observed for 10 time points were required to reach a power of 80 % and a two-tailed significance level of 0.05.

2.4. Statistical analysis

To describe the parameter in study, measures at each time point are presented in terms of mean and relative 95 % confidence intervals. Comparisons at corresponding time points were performed using the non-parametric paired Wilcoxon test. The differences in variation over time separately for the two treatment regimens of the parameters in the study were evaluated performing Anova for repeated measure models or the non-parametric Friedman test for the non-gaussian distributed parameters INCAT and MRC.

In order not to overestimate the beta error, the alpha levels were not adjusted for multiple comparisons.

The Statistical Package for Social Sciences 24.0 (SPSS, SPSS Inc., Chicago, IL) was

used for all analyses.

3. Results

Ten patients fulfilled the inclusion/exclusion criteria and were enrolled in the study. Data were collected from each patient during an 8-month follow up period.

Table 1 summarizes the patients' main clinical and demographic characteristics at baseline.

The patients' age ranged from 25 to 71 years and the disease durations from 4 to 19 years.

The efficacy scales INCAT, MRC, ROD-S, and GS show a

Table 1
Clinical and demographic data. All the values, except gender, are reported at entry as mean ± standard deviation (range).

	Patients (n = 10)
Gender (men/women)	4/6
Age (years)	48.3 ± 15.44 (25–71)
Disease duration (years)	9.6 ± 4.99 (4–19)
Age at onset (years)	38.7 ± 14.61 (14–54)
Weight (kg)	60.3 ± 4.32 (55–65)
Dose g/kg/month (SCIg = MPT)	1 ± 0.07 (0.92–1.09)
INCAT	2.4 ± 1.35 (0–4)
MRC	76.4 ± 4.59 (68–80)

nonsignificant variation between the groups, both when considering all the period from T0 to T4 (repeated measures ANOVA/Friedman test), and just T0 versus T4 (INCAT $p = 0.15$; MRC $p = 0.49$; R-ODS = 0.43; GS = 0.61)

Regarding IgG plasma concentration, a mean variation of 5.4 % in the group treated with MPT ($p = 0.15$) versus a negative variation of 4.3 % in the group who used pump administration was observed (Fig. 1).

LQI sub-scale I (treatment interference) significantly improved in the MPT period ($p = 0.02$). Conversely, the other dimensions of LQI sub scale (i.e., "therapy-related problems", "therapy setting", and "treatment costs") showed no statistically significant differences. All patients using MPT were able to prepare and infuse at home their subcutaneous immunoglobulin doses in 10 min or less, whereas the mean duration of pump infusion and preparation was 75 min (range: 70–85 min). All patients were able to self-injected the therapy after a mean of two session of nurse's training.

There were no cases of drop-out or dose adjustment during follow-up and none of them had any adverse events.

4. Discussion

This is a proof-of-concept study of CIDP patients who were IgG therapy responders self-administering SCIg via MPT or infusion pump. This is, to our knowledge, the first study on SCIg administered via MPT in CIDP patients.

All enrolled patients were IgG therapy responders and had received SCIg for 3 months prior to enrollment at a similar monthly dose as the last IVIG infusion. Our study shows that, at least in the short term, infusion pump and MPT are equally effective in CIDP patients, as demonstrated with the clinical evaluation performed using the INCAT, MRC, R-ODS, and GS scales.

In addition, MPT improves the QoL, as demonstrated by improvement in the LQI sub-scale I (treatment interference), which could be due to the shorter time required for preparation and administration.

We also found an increase of 5.4 % ($p = 0.15$) in plasma IgG levels in the MPT period compared to the infusion pump period (Fig. 1). Our data suggest that frequent administration of small doses delays IgG clearance, and thus increases plasma levels.

The use of MPT in PIDD patients has been well reported. A retrospective medical record review [11] analyzed data on 173 PIDD patients who self-administered SCIg via infusion pump or MPT. In this study, the mean serum IgG levels were higher among MPT users than pump users, which is similar to our findings.

It is well documented that the IgG catabolism rate is proportional to its serum level, which is a unique phenomenon restricted to this immunoglobulin class [14]. Therefore, the initial high peak level after IVIg infusion induces a greater IgG catabolic clearance rate. Since SCIg is generally administered weekly or more frequently, the IgG dose is absorbed and redistributed much more slowly, which results in less fluctuation of serum IgG levels [15].

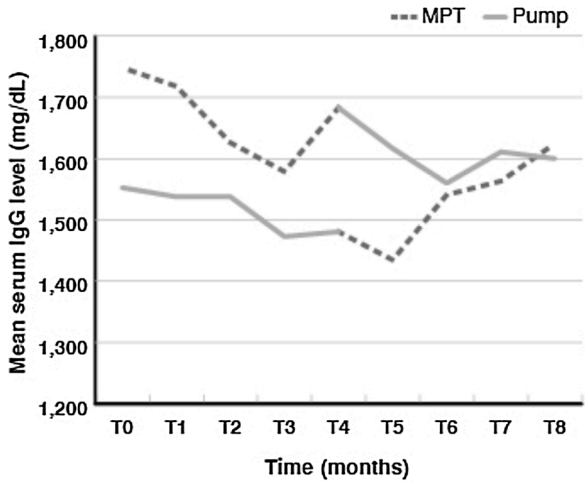

Fig. 1. Mean serum IgG levels during MPT (manual push technique) therapy and infusion pump period, from T0 (beginning of therapy with that technique) to T4 (four months from beginning of therapy with that technique).

Therefore, we suggest that MPT may grant stable plasma IgG levels, avoiding the wear-off effect due to lengthy administration (Fig. 1).

However, it is still uncertain whether high trough or peak levels are more effective in IgG therapy for CIDP, even if the recent study of Markvardsen et al. found that in patients with CIDP receiving SCIg or IVIg, changes in plasma IgG levels during treatment did not correlate with changes in muscle strength or other motor performance skills [16].

Our study shows that MPT slightly increases plasma IgG levels with respect to infusion pump and maintains clinical effectiveness.

This proof-of-concept study has some limitations, mainly involving the study design (in particular the absence of blindness), the small sample size (a hurdle difficult to overcome, given the rarity of CIDP), and the short treatment period.

Further studies with larger samples sizes and longer follow-up periods are needed to confirm these findings.

5. Conclusions

CIDP patients included in this study had documented clinical response to IVIg with evidence of wear-off effect. Before entering this study, patients were administered SCIg therapy for at least three months, as replacement for the previous IVIg treatment.

MPT technique, which is widely used in PIDD patients, in our group proved as effective as the traditional subcutaneous administration with pump, with improved QoL.

In addition, we detected a slight increase in plasma IgG levels during MPT therapy period in comparison with pump infusion period.

Our proof-of-concept study highlights the feasibility of MPT in stabilizing symptoms in CIDP patients. The slight increase in plasma IgG levels obtained with this technique, if confirmed by further study with greater sample sizes, may allow the reduction in individual doses, with obvious repercussions on the cost of therapy.

Funding

Publishing support and journal styling services were provided by SE*Ed* Medical Publishers and funded by CSL Behring, Italy. The sponsor had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript. Associazione Neuropatie Croniche Piemonte, Italy financially supported the study investigators (partly).

Data statement

The data that support the findings of this study are available in the supplementary material of this article.

CRediT authorship contribution statement

Dario Cocito: Conceptualization, Methodology, Writing - original draft, Supervision, Funding acquisition. **Erdita Peci:** Data curation, Supervision. **Simona Rigaldo:** Project administration. **Carlotta Canavese:** Project administration. **Giuseppe Migliaretti:** Formal analysis. **Federico M. Cossa:** Supervision.

Declaration of Competing Interest

DC received honoraria for lecturing from Baxter, CSL Behring, and Kedrion; he received personal compensation for serving on the Advisory Board of CSL Behring, Kedrion and travel grants to attend scientific

meetings from Baxter, Kedrion, and CSL Behring.

EP reports travel grants to attend scientific meetings from CSL Behring and Kedrion. SR reports travel grants to attend scientific meetings from CSL Behring and Shire Italia S.p.A.CC, GM and FMC report no disclosures.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2020.106240.

References

[1] J.M. Vallat, C. Sommer, L. Magy, Chronic inflammatory demyelinating polyradiculoneuropathy: diagnostic and therapeutic challenges for a treatable condition, Lancet Neurol. 9 (2010) 402–412.

[2] M.P. Lunn, H. Manji, P.P. Choudhary, R.A. Hughes, P.K. Thomas, Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England, J Neurol Neurosurg Psychiatry 66 (1999) 677–680.

[3] M.M. Mehndiratta, R.A. Hughes, Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy, Cochrane Database Syst. Rev. (9) (2012). CD003906; doi: 10.1002/14651858.CD003906.pub3. Update in: Cochrane Database Syst Rev 2015; (8):CD003906.

[4] R.A. Hughes, M.M. Mehndiratta, Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy, Cochrane Database Syst. Rev. (8) (2012). CD002062; doi: 10.1002/14651858.CD002062.pub2. Update in: Cochrane Database Syst Rev 2015; 1:CD002062.

[5] F. Eftimov, J.B. Winer, M. Vermeulen, R. de Haan, I.N. van Schaik, Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy, Cochrane Database Syst. Rev. (2013) 12. CD001797.

[6] E. Nobile-Orazio, D. Cocito, S. Jann, et al., IMC Trial Group. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial, Lancet Neurol. 11 (2012) 493–502.

[7] E. Nobile-Orazio, D. Cocito, S. Jann, et al., IMC Trial Group. Frequency and time to relapse after discontinuing 6-month therapy with IVIg or pulsed methylprednisolone in CIDP, J Neurol Neurosurg Psychiatry 86 (2015) 729–734.

[8] D. Cocito, A. Merola, A. Romagnolo, et al., Subcutaneous immunoglobulin in CIDP and MMN: a different long-term clinical response? J Neurol Neurosurg Psychiatry 87 (2016) 791–793.

[9] L.H. Markvardsen, J.C. Debost, T. Harbo, et al., Danish CIDP and MMN Study Group. Subcutaneous immunoglobulin in responders to intravenous therapy with chronic inflammatory demyelinating polyradiculoneuropathy, Eur. J. Neurol. 20 (2013) 836–842.

[10] I.N. van Schaik, V. Bril, N. van Geloven, et al., PATH study group. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Neurol. 17 (2018) 35–46, doi: 10.1016/S1474-4422(17)30378-2. Erratum in: Lancet Neurol 2018; 17: 26. Lancet Neurol 2018; 17:661.

[11] R.S. Shapiro, Subcutaneous immunoglobulin therapy given by subcutaneous rapid push vs infusion pump: a retrospective analysis, Ann. Allergy Asthma Immunol. 111 (2013) 51–55.

[12] M. Berger, T. Harbo, D.R. Cornblath, O. Mielke, IgPro20, the Polyneuropathy and Treatment with Hizentra® study (PATH), and the treatment of chronic inflammatory demyelinating polyradiculoneuropathy with subcutaneous IgG, Immunotherapy 10 (2018) 919–933.

[13] P.Y. Van den Bergh, R.D. Hadden, P. Bouche, et al., European Federation of Neurological Societies; Peripheral Nerve Society. 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 - first revision, Eur. J. Neurol. 17 (2010) 356–363, https://doi.org/10.1111/j.1468-1331.2009.02930.x. Erratum in Eur J Neurol 2011;18:796.

[14] E.D. Lobo, R.J. Hansen, J.P. Balthasar, Antibody pharmacokinetics and pharmacodynamics, J. Pharm. Sci. 93 (2004) 2645–2668.

[15] F.A. Bonilla, Pharmacokinetics of immunoglobulin administered via intravenous or subcutaneous routes, Immunol. Allergy Clin. North Am. 28 (2008) 803–819.

[16] L.K. Markvardsen, S.B. Sørensen, I. Christiansen, et al., Retrospective correlation analysis of plasma Immunoglobulin G and clinical performance in CIDP, PeerJ 7 (2019) e6969.