RESEARCH REPORT

A smooth transition protocol for patients with multifocal motor neuropathy going from intravenous to subcutaneous immunoglobulin therapy: an open-label proof-of-concept study

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Abstract Intravenous immunoglobulin (IVIG) is the first-line therapy for multifocal motor neuropathy (MMN). This open-label multi-centre study (NCT00701662) assessed the efficacy, safety, and convenience of subcutaneous immunoglobulin (SCIG) in patients with MMN over 6 months, as an alternative to IVIG. Eight MMN patients (42–66 years), on stable IVIG dosing, received weekly SCIG at doses equivalent to previous IVIG using a ''smooth transition protocol''. Primary efficacy endpoint was the change from baseline to week 24 in muscle strength. Disability, motor function, and health-related quality of life (HRQL) endpoints were also assessed. One patient deteriorated despite dose increase and was withdrawn. Muscle strength, disability, motor function, and health status were unchanged in all seven study completers who rated home treatment as extremely good. Four experienced 18 adverse events, of which only two were moderate. This study suggests that MMN patients with stable clinical course on regular IVIG can be switched to SCIG at the same monthly dose without deterioration and with a sustained overall improvement in HRQL.

Key words: disability, intravenous immunoglobulin, multifocal motor neuropathy, muscle strength, subcutaneous immunoglobulin

Introduction

Multifocal motor neuropathy (MMN) is an immune-mediated, predominantly demyelinating neuropathy, characterised by slowly progressive muscle weakness in one or more limbs, without associated sensory loss and with mild muscle wasting related to strength loss. In four randomised trials, high-dose intravenous immunoglobulin (IVIG) has been shown to be effective in MMN *(Joint Task Force of the EFNS and the PNS, 2006)*. IVIG is currently the first-line treatment with an approximately 80% response rate *(van Schaik et al., 2005)*.

Subcutaneous formulations of immunoglobulin (SCIG) have been demonstrated to be as effective as IVIG for replacement therapy in patients with immunoglobulin deficiency *(Chapel et al., 2000)*. One advantage of SCIG infusion is that it can be self-administered in a home setting. SCIG is largely free of the adverse effects associated with high-dose IVIG. Once a steady state is achieved, SCIG leads to stable

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serum immunoglobulin G (IgG) levels in contrast to the peaks and troughs associated with IVIG.

Two recent reports suggest that SCIG therapy is equally effective as IVIG in sustaining muscle strength in patients with MMN *(Eftimov et al., 2009; Harbo et al., 2009)*. We report our experience with a ''smooth transition protocol'' for switching patients from IVIG to SCIG.

Materials and Methods

Patients

Eight adults (4 women and 4 men; age range 42–66 years) with MMN being treated with IVIG were enrolled. Patients who had previously responded to IVIG were included in this study if they fulfilled the following criteria: a documented clinical diagnosis of MMN supported by electrophysiological evidence of conduction block; stable clinical disease without deterioration of muscle strength whilst on regular IVIG at a dose of 0.4–2 g/kg/month for ≥12 weeks before inclusion; and provision of informed consent.

Patients were excluded from this study if they were on an IVIG dose <0.4 g/kg/month or >2 g/kg/month; had serum transaminases >2.5 times the upper limit of normal (ULN) or creatinine >1.5 times the ULN; had known allergic reaction to blood products; had any skin disease interfering with the assessment of injection-site reactions; or had participated in a study of an investigational drug within the last 3 months.

This study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki (NCT00701662). This study protocol and all other study documents were approved by the relevant Independent Ethics Committees. Patients provided signed informed consent before entering this study.

Study design

This was a prospective, open-label, multi-centre proof-of-concept study, conducted at three centres between November 2007 and January 2009. Vivaglobin® (CSL Behringc GmbH, Marburg, Germany) was the SCIG product used.

To ensure dose equivalence, each patient's total SCIG monthly dose was calculated based on their average monthly IVIG dose, obtained by dividing the cumulative IVIG dose over the preceding 3 months by three. The weekly SCIG dose was calculated by dividing the average monthly IVIG dose by four. Patients were switched from IVIG to SCIG using a ''smooth transition protocol'' in the following manner: during the first SCIG infusion (week 1), 25% of the total weekly SCIG dose was administered on the same day as the last IVIG dose. In week 2, 50% of the total weekly SCIG dose was administered, followed by 100% of the dose (maintenance dose) in week 3. Patients continued with 100% of the weekly dose until study end. The duration of treatment was 24 weeks, comprising a period from weeks 1 to 8 that constituted the IVIG wash-out phase overlapping with SCIG wash-in, and 16 weeks of SCIG self-infusion (Fig. 1).

During weeks 1–4, patients were trained to self-administer SCIG using a battery-driven infusion pump (Crono Super PID 20 ml) before switching to self-infusion at home during weeks 5–24. During the first SCIG infusion (week 1), the maximum volume per infusion site was 20 ml administered at a rate of up

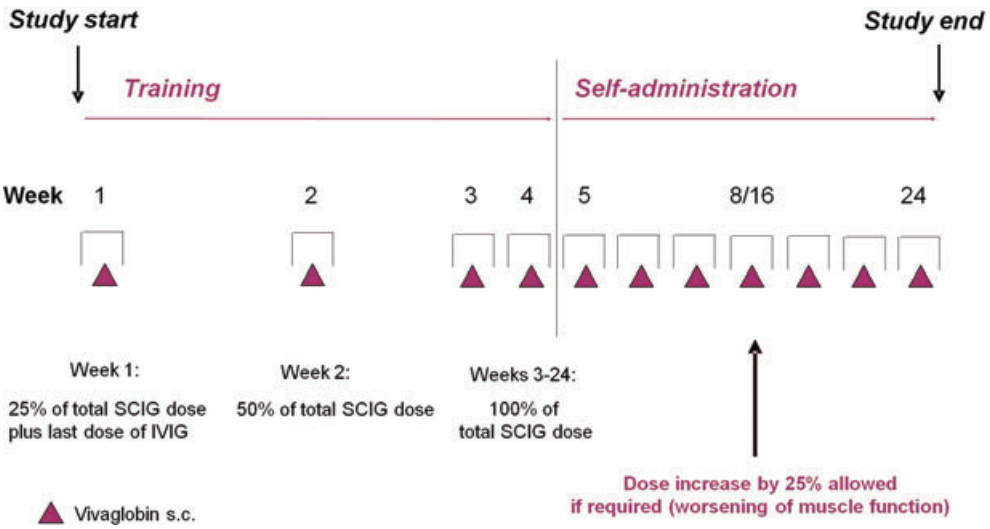

Figure 1. Study design. The smooth transition protocol included gradual switch from intravenous immunoglobulin to subcutaneous immunoglobulin.

to 22 ml/h, with a stepwise increase to a maximum of 40 ml at a rate of 35 ml/h.

Dose increase by 25% was allowed if worsening of muscle strength (≥2 points), neurological disability (≥1 point), and motor function (≥1 point) occurred simultaneously (Fig. 1).

Primary outcome measure

The primary efficacy endpoint was the change in muscle strength between baseline and week 24 in the intention-to-treat (ITT) dataset. Muscle strength was measured using a modified Medical Research Council (MRC) scale *(Paternostro-Sluga et al., 2008)*. Muscle strength was measured in 20 muscle groups on each side of the body (40 muscle groups per patient). The maximum possible MRC score for an individual patient was thus 200. Muscle strength was determined at screening and before SCIG infusions at weeks 8, 16, and 24. Additional assessments were performed at week 12 or 20 for patients who had dose adjustments (Fig. 1). Assessments in an individual patient were performed by the same assessor throughout this study.

Secondary outcome measures

An overall assessment of disability using a modified Guy's neurological disability scale *(Sharrack and Hughes, 1999)* was assessed at weeks 8, 16, and 24.

Motor function was assessed using a non-validated individual motor function score based on the ease of performance of four daily tasks (e.g., shaving) involving the affected muscle groups, as specified by each patient at baseline *(Leger et al., 2001)*. Individual motor function scores were recorded at screening and week 1, and thereafter at fortnightly intervals until Completion Visit (week 25).

Health-related quality of life (HRQL) was measured at screening and week 25 using the following assessment tools: a questionnaire about the current IgG therapy to evaluate the patients' perceptions about their SCIG treatment, the Life Quality Index (LQI), and a visual analogue scale (VAS) to assess the global health status.

Safety and tolerability assessments

Safety variables included overall rate, severity, and treatment relatedness of any adverse event (AE) per SCIG infusion and per patient; assessment of local tolerability; and changes in routine laboratory parameters or vital signs.

Laboratory measurements

Routine haematology, chemistry, and urinalysis were performed at screening and the Completion Visit (week 25). The total serum IgG levels were determined before and after last IVIG treatment, before infusion at weeks 8 and 16, and at the Completion Visit (week 25).

Statistical methodology

Analysis of muscle strength (primary efficacy endpoint) between baseline and week 24 of the study was performed on the ITT population, using descriptive statistics and nonparametric, two-sided 95% confidence intervals (CI) based on the Hodges–Lehmann method. The ITT population comprised all patients who received the study drug and had at least one post-baseline value for muscle strength.

Secondary outcome measures were analysed in the ITT population using descriptive statistics. For the disability score and individual motor function assessment, nonparametric, two-sided 95% CI based on the Hodges–Lehmann method was calculated.

Mean IgG levels were calculated for the ITT population. Because one baseline value was missing, the baseline mean IgG level was calculated for seven patients. The IgG levels of patient B at weeks 16 and 24 were missing; a last observation carried forward analysis was applied to calculate the mean IgG levels of the ITT population at these time points.

Results

Patients

The baseline characteristics of the eight patients with MMN enrolled in this study are summarised in Table 1.

Study drug administration

All patients received the planned eight weekly infusions during the wash-in/wash-out phase (weeks 1–8). In the efficacy phase (weeks 9–24), an additional 16 weekly infusions per patient were planned. The first five infusions were administered to all patients; the subsequent 11 were administered to seven of eight patients. Patient B was considered a non-responder per study protocol and therefore did not receive the final 11 infusions. Patients A and B had dose adjustments (25% increase) of SCIG.

The total number of infusions administered was 183. The mean weekly SCIG dose was 271.8 ± 139.13 mg/kg (range 100–488 mg/kg).

Efficacy

Muscle strength, motor function, and disability

There was no overall change in muscle strength (MRC score mean change: 0.4; 95% CI −4.50 to 5.00) (Fig. 2), motor function (individual motor function score mean change: 0.4; 95% CI −1.50 to 0.75), and disability

Table 1. Baseline characteristics of study patients.

Patient	Gender	Age (years)	Body mass index (kg/m^2)	Duration of multifocal motor neuropathy since diagnosis at study entry (years)	Dose of IVIG at study entry (g/kg/month)	Serum immunoglobulin G level preceding last IVIG infusion (g/l)
A	Male	62	21.3	9.4	1.0	15.40
B	Female	42	16.3	9.0	1.0	18.88
C	Female	65	31.2	4.1	0.44	13.20
D	Female	49	23.4	4.8	1.6	15.70
E	Male	53	32.2	4.3	0.8	11.60
F	Male	66	24.2	4.0	0.49	Missing data
G	Male	65	35.1	4.8	1.0	23.9
H	Female	56	23.9	9.7	1.9	23.9
Mean	–	57.25	25.95	6.3	1.2	17.5

IVIG, intravenous immunoglobulin.

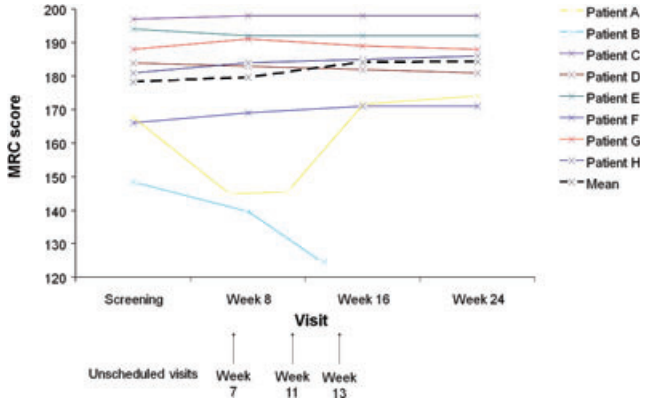

Figure 2. Muscle strength over time. Individual and mean values (n = 8) are shown. The scheduled visits for assessment of muscle strength in both upper and lower limbs were at screening and weeks 8, 16, and 24. Patients A and B had unscheduled visits due to worsening of symptoms.

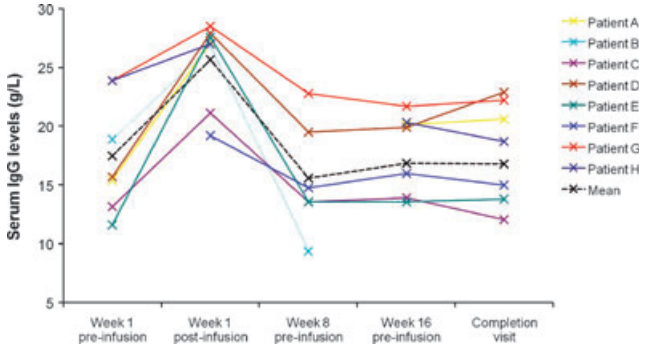

Figure 3. Serum immunoglobulin G (IgG) levels over time. IgG levels were determined before and after the last intravenous immunoglobulin treatment, before infusion at weeks 8, 16, and 25. Shown here are individual and mean values (n = 8).

(Guy's disability score mean change: 0.1; 95% CI 1.00 to 0.00).

Health-related quality of life

Patients' satisfaction with this IgG treatment remained unchanged or improved when treatment setting was changed from hospital/doctor's office to home. There was improvement in total LQI score in six of eight patients at the Completion Visit. The health status, as assessed by VAS, was maintained or improved slightly in all seven patients with available data. All seven patients who completed this study chose to continue with SCIG treatment at study end. There were no HRQL data for the sole withdrawn patient (patient B).

Serum IgG levels

The mean (±SD) serum IgG trough level preceding the last IVIG infusion was 17.5 g/l (± 4.9) for the ITT population compared with a mean of 16.8 g/l (± 5.0) at the end of 24 weeks of SCIG (Fig. 3). Therefore, with the exception of the withdrawn patient, SCIG infusions led to stable serum IgG trough levels comparable with the last IgG trough level achieved by patients whilst on IVIG.

Despite administration of an equivalent dose of SCIG and subsequent dose increase, IgG levels for patient B at week 8 remained at 9.35 g/l (compared with 18.9 g/l whilst on IVIG), which was associated with deterioration in muscle strength. The patient was returned to IVIG treatment with consequent normalisation of her IgG levels.

Safety and tolerability

Four of eight patients (50%) experienced a total of 18 AEs (0.098/infusion). Except for two moderately severe events, all AEs were of mild intensity (Table 2).

The most frequent AEs were reactions associated with the injection site, including oedema, pruritus, and skin reaction, each reported four times by patient C (Table 2). All of these reactions, which were temporally associated (within 24 h) with treatment and were

Table 2. All AEs and rates.

Events	Patient	Severity	Number of AEs (rate)*
Local reactions			
Injection-site edema	C	Mild	4 (0.022)
Injection-site pruritus	C	Mild	4 (0.022)
Injection-site skin reaction	C	Mild	4 (0.022)
General reactions			
Asthenia	D	Mild	1 (0.005)
Erythema	A	Mild	1 (0.005)
Orchitis	A	Mild	1 (0.005)
Hemicephalalgia	A	Mild	1 (0.005)
Influenza	H	Moderate	1 (0.005)
Spontaneous haematoma	C	Moderate	1 (0.005)

AE, adverse event.
*Rates (number per infusion) based on total of 183 infusions.

designated by the investigator as treatment-related, were transient and of mild intensity.

General reactions, which included asthenia, erythema, orchitis, hemicephalalgia, influenza, and spontaneous haematoma, were not considered to be treatment-related (Table 2). Erythema, hemicephalalgia, and spontaneous haematoma were temporally associated with treatment. Beside influenza and spontaneous haematoma, which were of moderate severity, all other events were mild (Table 2). The events of influenza and spontaneous haematoma resolved after treatment with symptomatic measures and local ice pack, respectively. There was no other event with at least possible relation or temporal association to treatment.

There were no serious AEs or AEs leading to discontinuation of SCIG.

Discussion

Seven of eight patients with MMN in this study could be switched from IVIG to equivalent doses of SCIG, using a ''smooth transition protocol'', without deterioration. Most patients reported improved HRQL indices during SCIG treatment, which is consistent with the experience with IgG replacement in patients with primary immunodeficiency *(Gardulf et al., 2004; Nicolay et al., 2006)*. The treatment was well tolerated, with no serious AEs and most events being local reactions of mild severity. All seven patients who completed this study chose to continue on SCIG rather than revert back to IVIG. Furthermore, with the weekly regimen of SCIG administration, end-of-dose-interval worsening as is observed in some patients on IVIG with longer dosing intervals *(Harbo et al., 2009)* could be avoided.

Our findings are consistent with those of Harbo *et al. (2009)* and Eftimov *et al. (2009)* in showing that SCIG can be as effective as IVIG at preserving muscle strength if an equivalent dose is used. This is an important practical point illustrated by the sustained deterioration in muscle strength experienced by four patients in the study by Eftimov *et al. (2009)* who received SCIG doses equivalent to 50% of their previous IVIG dose.

Two patients in our study had dose increases because of worsening of muscle strength and disability after SCIG initiation; one (patient A) subsequently improved *(Dacci et al., 2010)*, but the other (patient B) deteriorated further and was considered a non-responder and had to be withdrawn from this study. The latter patient had low IgG levels (9.35 g/l, compared with an IgG level of 18.9 g/l whilst on IVIG), despite infusion of an equivalent dose of SCIG and further dose increases. It is unclear whether the low body mass index of this patient (16.3 kg/m^2) contributed to poor absorption of SCIG. She has successfully reverted back to IVIG treatment and is currently stable. All other patients receiving SCIG had serum IgG levels comparable with the last trough IgG level whilst on IVIG. Although a direct relationship between serum IgG levels and response to treatment has not been established for chronic autoimmune neuropathies, such as MMN and chronic inflammatory demyelinating polyneuropathy, there is evidence to suggest that the change in serum IgG levels achieved with IVIG treatment may affect the outcome in patients with acute Guillain-Barré syndrome *(Kuitwaard et al., 2009)*. In this context of switching route of IgG administration in patients previously stable on IVIG, the achievement of comparable serum IgG levels with SCIG is likely to be an important determinant of success.

In patients with immune deficiencies, home-based SCIG therapy is associated with reduced healthcare costs and resource use compared with IVIG *(Hogy et al., 2005)*, as it avoids visits to hospitals or doctors' offices and nursing visits *(Misbah et al., 2009)*. At least theoretically, this should also be true for patients with MMN, although no pharmacoeconomic analyses have yet been conducted.

The main limitation of our study was the small number of patients which was similar to that of other studies and understandable in the context of the rarity of MMN.

We have shown that, using a ''smooth transition protocol'', it is feasible to switch over patients with MMN from IVIG to SCIG while sustaining improvements in muscle strength as seen with IVIG. Future developments in SCIG delivery, such as the use of 20% formulations *(Misbah et al., 2009)*, are

likely to enable administration of even higher doses of IgG using the subcutaneous route. The efficacy of SCIG in MMN, its relative lack of systemic adverse effects, its acceptability and even preference over IVIG by patients is likely to be extendable to other autoimmune neuropathies, and thus provides patients with an effective alternative to IVIG.

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