Randomized trial of facilitated subcutaneous immunoglobulin in multifocal motor neuropathy

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Great Minds.
RANDOMIZED TRIAL OF FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN IN MULTIFOCAL MOTOR NEUROPATHY

Running title: A Randomized Non-inferiority Cross-over Trial

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Randomized controlled, Immunoglobulin, treatment

ABSTRACT

Objective: To optimize subcutaneous therapy with immunoglobulins we compared large volume infusion of IgG facilitated by pretreatment with hyaluronidase (fSCIG) to conventional infusion of multiple small dosages (cSCIG) in 20 patients with multifocal motor neuropathy (MMN).

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Methods: A randomized, non-inferiority and observer-blinded cross-over design was applied with a treatment period of 24 weeks at each therapy.

Results: In 18 patients fSCIG was feasible, 2 patients leaving the study due to side-effects. The primary study variable, isometric strength, was unchanged, being 100.8% (95% CI: 94.8% – 107.1%) in fSCIG and 105.9% (95% CI: 99.8% – 112.0%) in cSCIG. Secondary end-points of disability, functions, impairments and quality of life showed no differences between the two treatments. Mild and short-lasting generalized side-effects were similar in the two groups, whereas the relative frequency of localized side-effects at the injection site was increased after fSCIG (0.63 (95% CI: 0.23 – 1.00) vs 0.09 (95% CI: 0.00 – 0.22), P =0.005). The preference of the patients favoured fSCIG for 2 out of 5 VAS-scores as well as the total mean score of all preferences (P =0.03).

Conclusions: fSCIG seems effective, feasible and safe. In addition, it is preferred by patients but is accompanied by a higher frequency of short lasting localized side-effects.

Clinicaltrials.gov: NCT02556437

European Clinical Trials Database: 2015-003453-18

INTRODUCTION

Treatment with IgG-immunoglobulins is effective for the maintenance of motor function in patients with multifocal motor neuropathy (MMN)(1). Administration with either intravenous infusion of large volumes of immunoglobulins monthly or with subcutaneous infusion of multiple small volumes 2 – 3 times weekly are commonly applied techniques that appear to be equally effective.
The advantage of subcutaneous therapy is that infusions can be performed at home without the need for supervision(2), but frequent small infusions are time consuming and troublesome. Home based treatment with immunoglobulins would, therefore, be more attractive if a technique that allows the infusion of larger volumes was available.

Pretreatment with hyaluronidase allows subcutaneous infusions of large volumes of immunoglobulins and is applied in primary immune deficiency disorder (PID) and in other pediatric disorders, as well(3,4). Therefore, we studied the efficacy, feasibility, safety and preference of immunoglobulin therapy facilitated by pretreatment with hyaluronidase (fSCIG) in a non-inferiority trial of patients with MMN already treated with multiple small subcutaneous infusions of immunoglobulin (cSCIG).

MATERIALS AND METHODS

Study design

We hypothesized that fSCIG is as effective as cSCIG applying a non-inferiority design. Efficacy, feasibility, safety and preference of fSCIG were compared to those of cSCIG in MMN patients already treated with cSCIG in a block randomized cross-over trial. The study period was 48 weeks with 24 weeks at each treatment. A previous study showed that MMN patients lost 16% of muscle strength after a 19% prolongation of the treatment interval(5). Taking this observation into consideration together with the constant need for maintenance therapy in MMN it was decided not to include a wash-out period.
The study included participants from three Danish neurological university clinics in Aarhus, Odense and Copenhagen. Evaluation and supervision of home-based treatment took place at the Neuromuscular Out-Patient Clinic, Rigshospitalet in Copenhagen or at the Neuromuscular Clinic, Aarhus University Hospital in Aarhus.

The local ethics committee of the Capital Region, The Danish Medicines Agency and The Danish Data Protection Agency approved the study, which was registered at clinicaltrials.gov (NCT02556437) and at the European Clinical Trials Database (2015-003453-18) and was monitored by the local Good Clinical Practice (GCP) units at the sites according to international guidelines. Written informed consent was obtained from all patients participating in the study.

Participants

Inclusion criteria were a diagnosis of MMN according to the EFNS/PNS criteria(6), age of 18 years or more and maintenance therapy with cSCIG at a stable dose for at least 3 months prior to study.

Exclusion criteria were other neuropathies, treatment with other immune modulating therapies within the last six months, breastfeeding and pregnancy.

The randomization sequence was generated from randomization.com and the study nurses at the site of the principal investigator allocated therapy according to the generated list. Enrollment of patients was performed by the study investigators. Patients were recruited from February 2016 to February 2017.
Treatments

The same dose of immunoglobulin as used during the last three months before study was maintained in both treatment arms.

Recombinant human hyaluronidase was manually injected at a dose of 80 U/g IgG followed by infusion of a 10% solution of human normal immunoglobulin (HyQvia, Shire, Lexington, MA) using an electronic peristaltic pump (Mini Rythmic PN+ R, Micrel Medical Devices, Greece). The maximum volume infused at one site was 600 ml at a rate of 300 ml/hour.

Conventional SCIG was infused at a concentration of 16% human normal immunoglobulin (Subcuvia, Shire, Lexington, MA) at the abdomen or the thighs using 1 or 2 mechanical pumps (Freedom Pump), one or two 60 ml syringes and a maximum of 4 subcutaneous lines per pump. The average infusion speed was 20 ml/hour with a maximum infusion volume of 20 ml at each site.

In case of clinical worsening defined by an increase of 1 point or more of the Overall Disability Sum Score (ODSS) or by a reduction of 50% of grip strength, the treatment dose was increased by 25%.

Efficacy, Feasibility, Safety and Patient Preference

Patients were evaluated by the same blinded rater (AA) and interviewed by the study nurses regarding feasibility, safety and side-effects at inclusion as well as after 12, 24, 36 and 48 weeks.

Because of the limited number of patients the primary end-point was isometric muscle strength (IMS), which has a high sensitivity for therapeutic effects as compared to the overall
disability sum score. Two major joints including four weakened muscle groups were selected individually using a Biodex System PRO 3/4 dynamometer (Biodex Medical Systems, Inc. N.Y., N.Y., USA), the values being normalized to baseline(7).

As secondary end-points, data for the following impairments, functions and disabilities were included: Disability (ODSS), manual assessment of muscle strength (Medical Research Council (MRC, 0-90)), grip strength using a hand held dynamometer (JAMAR R, Sammons Preston Roylan, Chicago, IL), dexterity (9 Hole Peg Test (9-HPT)), walking performance (Six Spot Step Test (SSST)(8)) and quality of life (EQ-5D-5L Index Value and EQ-5D-5L VAS score).

For evaluation of preference for the two therapies, patients were asked to compare fSCIG and cSCIG at five VAS scales for the following issues: Preference, easiness of administration of infusion, maintenance of a normal life, side-effects and overall satisfaction. The five VAS scales were straight lines without numbers, the two therapies being placed at each end.

Blood was collected for evaluation of the presence of indicators of hemolytic anemia performed at start and after the last infusion in each treatment arm as well as halfway through the fSCIG treatment period at day 1, 7 and 14 after infusion. IgG levels were determined at the same intervals.

**Statistics**

Sample size was calculated based at a non-inferiority criterion using a 0.05 level of significance, a power of 0.9 and an expected standard deviation of 20%. Based on earlier studies demonstrating the high sensitivity of IMS in comparison to other clinical
observations(9), the non-inferiority margin was chosen as a 15% change in muscle strength(5). A minimum of 17 subjects were needed to fulfil these criteria.

The normality of distributions was assessed visually using quantile-quantile plots and data histograms. Gaussian data were analyzed using means and parametric statistics. Otherwise, data were described using medians and non-parametric statistics. Differences for the primary end-point from the visits were tested using a mixed model followed by Student’s paired t-test for differences at a 0.05 level of significance including evaluation of period effects. End visit values of secondary end-points and biochemical tests were compared with paired Student’s t-test, paired Wilcoxon signed-rank test or McNemar’s test. The preference values of the five VAS forms were transformed into numbers, -10 being the maximum value in favour of cSCIG, 10 the maximum in favour of fSCIG. Moreover, an overall mean score assembling the five issues was calculated. In addition, the primary end-point and all secondary variables of efficacy reported in table 2 were subject to non-inferiority testing using Student’s paired t-test, a non-inferiority margin of 15%, a 0.05 level of significance and the one side of a 90% CI as reported elsewhere(10).

Data are reported according to the CONSORT criteria(11). All statistical analyses were performed by AA using SAS software. The sponsor neither was involved in drafting of the manuscript nor in the data analysis.

RESULTS

Fig. 1 shows that 38 MMN patients treated with cSCIG were screened for study participation, 20 being included. Table 1 shows the demographics and the clinical data for the 20 participating patients. The individual mean total dose of immunoglobulin (IgG) including
rescue therapy was similar in the two study arms, being 668 g (95% CI: 525 g – 811 g) in fSCIG vs. 673 g (95% CI: 531 g – 815 g) in cSCIG, corresponding to 28 g IgG/week in both groups. Patients received 13 infusions during fSCIG therapy, while the mean number of infusions during cSCIG was 53.3 (95% CI: 42.1 – 64.5). The mean volume at each infusion procedure during fSCIG was 557 mL (95% CI: 438 mL – 676 mL) and 86 mL (95% CI: 64 mL – 108 mL) during cSCIG. According to the protocol, two patients at fSCIG and one patient at cSCIG qualified for an increase of the IgG dose.

Two patients left the fSCIG arm prematurely. One patient withdrew from study after 10 weeks of fSCIG therapy due to headache, nausea and an experience of subclinical infection not allowing values of efficacy and preference to be obtained. The other patient reported dizziness, headache and tiredness with mild elevation of hepatic transaminases (1 – 2 x upper level). After 18 weeks on fSCIG this patient was prematurely shifted to cSCIG followed by normalization of the level of transaminases and improvement of symptoms, allowing all study parameters to be recorded according to the intention-to-treat principle. In addition, one patient on fSCIG received only half of the dose prescribed during all 24 weeks.

**Efficacy**

Values for isometric strength are shown in Fig. 2 and 3 as well as in Table 2. As compared to baseline values the strength following fSCIG and cSCIG therapy were 100.8% (95% CI: 94.5% – 07.1%) and 105.9% (95% CI: 99.8% – 112.0%), respectively ($P = 0.10$). IMS values for fSCIG were not inferior to cSCIG ($P = 0.0014$). No period effect influencing IMS was observed ($P = 0.8$). Neither was a carry-over effect observed ($P = 0.6$).
Secondary parameters of efficacy are shown in Table 2. There were no differences of MRC, ODSS, SSST, 9-HPT, grip strength, EQ-5D-5L-VAS and EQ-5D-5L-Index value comparing fSCIG and cSCIG therapy. Inferiority testing confirmed non-inferiority of all variables following fSCIG in comparison to cSCIG.

The IgG-levels in the fSCIG group varied at day 1, 7 and 14 \( (P = 0.0006) \) with an elevation of IgG by 2.3 g/L (95% CI: 1.0 – 3.6) at day 7 as compared to day 1 \( (P = 0.003) \). This increase was not correlated to IMS at the end visit \( (P = 0.9) \). There was no difference of mid-interval plasma IgG-levels between the two therapies \( (P = 0.9) \). The transaminases LDH and ALAT were similar in the two groups at study end.

**Side-effects**

Generalized side-effects with headache or nausea were reported during both therapies, occurring at least once in 44% of patients during both therapies. There was a higher relative frequency of local side-effects per infusion of 0.63 (Inter Quartile Range (IQR): 0.23 – 1.00) in fSCIG as compared to 0.09 (IQR: 0.0 – 0.22) in cSCIG \( (P = 0.005) \). The absolute number of infusions with local side-effects were, however, similar in fSCIG and cSCIG \( (P > 0.99) \).

No serious side-effects occurred during or following self-infusion at home. Hemoglobin levels at day 7 following fSCIG infusion were 3% lower than during cSCIG, values being 8.9 mmol/L (95% CI: 8.4 mmol/L – 9.4 mmol/L) vs. 9.2 mmol/L (95% CI: 8.6 mmol/L – 9.7 mmol/L), respectively. No signs of biochemical hemolysis were detected. Neither were there any differences of hemoglobin levels between the two therapies at any time tested.
Patient Preference

Fig. 4 shows the VAS scores reflecting the preferences of the patients. Comparing the two therapies fSCIG was preferred to cSCIG at the scores for maintaining a less disease dominated life style ($P = 0.0001$) and for easiness of IgG administration ($P = 0.006$). The mean score of all five VAS scores favoured fSCIG ($P = 0.03$). Dose of immunoglobulins did not influence patient satisfaction ($P = 0.2$).

DISCUSSION

The findings of the present study indicate that fSCIG therapy is effective, feasible and safe in MMN patients previously treated with cSCIG. We could not demonstrate any difference of efficacy between the two therapies, IMS being 100.8% (95% CI: 94.5% – 107.1%) in fSCIG and 105.9% (95% CI: 99.8% – 112.0%) in cSCIG. The significance of this finding was confirmed in a test of non-inferiority, also. Data were analyzed according to the intention to treat principle. Excluding the one patient who received half the prescribed IgG-dose during fSCIG increases the primary end-point value from 100.8% to 102.2%. However, given the relatively large statistical uncertainty with a difference of 1% in favour of fSCIG versus 11% in favour of cSCIG together with the use of a relatively large non-inferiority margin for non-inferiority testing, it cannot be excluded that cSCIG is slightly more effective than fSCIG using the same total dose of IgG. Preferably, a disability scale such as the ODSS which reflects the patients’ own perception of function should be applied as the primary outcome. However, due to the limited number of patients we chose a sensitive and objective measure of strength because weakness is the predominant impairment in MMN. The secondary endpoints of efficacy including MRC, ODSS, grip strength, 9HPT, SSST did not differ between the two
therapies, supporting our observation that fSCIG is as effective as cSCIG using the same dose.

In the present study of 20 MMN patients treated with fSCIG, two withdrew from study due to potential side-effects of IgG infusion. No serious complications to fSCIG therapy were observed in the present study neither of the cardiovascular, cerebrovascular or anaphylactic category, indicating a high degree of safety. Generalized side-effects including headache and nausea, showed similar frequencies in fSCIG and cSCIG.

Localized side-effects were relatively more frequent per infusion of fSCIG. Due to the high number of infusions of cSCIG, however, the absolute number of episodes with redness, itching, warmth, rash and tenderness at the injection sites were similar in the two groups. Similar observations for fSCIG treatment has been reported elsewhere(12), but the rate per infusion in fSCIG is somewhat higher than previously reported(3,12). Localized long-term complications of multiple fSCIG infusions in pediatric patients has not been reported in the literature(3,13). However, local effects following long-term administration of fSCIG at the doses used in MMN needs to be studied.

Based on the difference of bioavailability reported earlier of an increase of 93% at fSCIG as compared to 65-68% at cSCIG(3,14), we expected to observe higher IgG levels after treatment with fSCIG as compared to cSCIG. Such a difference was not observed, but we confirmed that IgG levels are higher at day 7 after infusion than at day 1(3).

The small but statistically significant drop in hemoglobin at day 7 during fSCIG as compared to cSCIG was not accompanied by any biochemical sign of hemolysis. There are several reports of treatment-related hemolysis in IVIG(15–17), but hemolysis has neither been reported in cSCIG(18) nor in fSCIG(3,12,18).
The scores for easiness of application, possibility for maintaining a normal life as well as the mean score for all five preferences of the patients significantly favoured fSCIG. In 11 out of 13 patients below the age of 60 a high satisfaction with fSCIG was reported, whereas five out of six patients with an age at sixty or above did prefer cSCIG. Potential explanations could be that the younger patients had less time to spend at home and that the elderly people had difficulties with handling of pump and utensils due to their longer disease duration. The Ig concentration in cSCIG used by most of our MMN patients in Denmark is somewhat lower than applied in some clinics (16% vs. 20%) leading to a moderate increase of volume and time of infusion. This might influence the degree of satisfaction with cSCIG. However, the treatment free interval is considerably longer using fSCIG than cSCIG independent of the IgG concentration applied.

We conclude that fSCIG therapy is feasible in the vast majority of MMN patients previously treated with cSCIG, that it increases local side-effects as compared to cSCIG, that it is effective for treatment of impairment, function, disability and quality of life and that patients favour pretreatment of IgG-infusion with hyaluronidase.

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DISCLOSURES:

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Figure legends

Figure 1
Title: Diagram of patient allocation.

Figure 2
Title: Mean isometric strength
Legend: Mean isometric strength for 19 MMN patients allocated at random to either fSCIG or cSCIG for 24 weeks followed by cross-over to the alternate therapy for further 24 weeks. The solid line represents mean IMS and the greyed region the 95% CI.

Figure 3
Title: Individual end-values of isometric strength
Legend: Paired individual end-values of isometric strength for 19 MMN patients allocated at random to either fSCIG or cSCIG for 24 weeks followed by cross-over to the alternate therapy for further 24 weeks.

Figure 4
Title: Preferences of patients for therapy.
Legend: VAS scores for the patient preference for fSCIG or cSCIG in 19 subjects receiving each therapy for 24 weeks, a zero-value indicating no preference, the top and bottom of the columns representing the 25 and 75 percentiles, the transverse bar the median, and the whiskers the highest and lowest values.

*P < 0.05
**P < 0.01
REFERENCES


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Table 1. Demographics and clinical characteristics in 20 patients with MMN at study start.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (95% reference interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.3 (30.2-78.4)</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>41.2 (24.6-57.8)</td>
</tr>
<tr>
<td>Duration of symptoms (years)</td>
<td>7.5 (5.3-21.0)</td>
</tr>
<tr>
<td>Duration of treatment (years)</td>
<td>4.5 (1.7-11.5)</td>
</tr>
<tr>
<td>Sex, M:F (n)</td>
<td>10:10</td>
</tr>
<tr>
<td>IgG (g/week)</td>
<td>26.2 (3.9-48.5)</td>
</tr>
<tr>
<td>MRC (0-90, au)</td>
<td>87.0 (82.5-89.0)</td>
</tr>
<tr>
<td>ODSS (0-12, au)</td>
<td>2.0 (2.0-4.0)</td>
</tr>
<tr>
<td>9-HPT (sec)</td>
<td>24.1 (18.3-31.4)</td>
</tr>
<tr>
<td>Grip strength (kgf)</td>
<td>20.8 (5.8-75.3)</td>
</tr>
<tr>
<td>SSST (sec)</td>
<td>6.2 (3.7-10.4)</td>
</tr>
<tr>
<td>EQ-5D-5L-Index value (0-1, au)</td>
<td>0.80 (0.75-0.92)</td>
</tr>
<tr>
<td>EQ-5D-5L-VAS (%)</td>
<td>85.0 (77.5-95.0)</td>
</tr>
</tbody>
</table>

*Median (IQR)
Table 2. Values for primary and secondary end-points of efficacy and quality of life in 19 MMN patients treated with fSCIG and cSCIG for 24 weeks each.

<table>
<thead>
<tr>
<th>End-point</th>
<th>fSCIG\textsubscript{12}\textsuperscript{a}</th>
<th>fSCIG\textsubscript{24}</th>
<th>cSCIG\textsubscript{12}\textsuperscript{a}</th>
<th>cSCIG\textsubscript{24}</th>
<th>p-value for superiority testing\textsuperscript{d}</th>
<th>p-value for non-inferiority testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized isometric strength (%)\textsuperscript{b}</td>
<td>101.5 (94.0-109.0)</td>
<td>100.8 (94.5-107.1)</td>
<td>103.2 (98.0-108.5)</td>
<td>105.9 (99.8-112.0)</td>
<td>0.10</td>
<td>0.0014</td>
</tr>
<tr>
<td>MRC (0-90, au)\textsuperscript{c}</td>
<td>88.0 (84.0-89.0)</td>
<td>88.0 (86.0-89.0)</td>
<td>88.0 (82.0-89.0)</td>
<td>87.0 (84.0-89.0)</td>
<td>0.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ODSS (0-12, au)\textsuperscript{c}</td>
<td>2.0 (2.0-4.0)</td>
<td>2.0 (2.0-4.0)</td>
<td>2.0 (2.0-4.0)</td>
<td>2.0 (2.0-4.0)</td>
<td>1.00</td>
<td>0.0007</td>
</tr>
<tr>
<td>9-HPT (sec)\textsuperscript{c}</td>
<td>23.8 (17.9-31.1)</td>
<td>25.4 (18.4-28.5)</td>
<td>22.1 (17.6-37.5)</td>
<td>24.8 (18.1-28.4)</td>
<td>0.51</td>
<td>0.0085</td>
</tr>
<tr>
<td>Grip strength (kgf)\textsuperscript{b}</td>
<td>23.0 (16.6-29.4)</td>
<td>23.7 (17.1-30.3)</td>
<td>23.1 (17.2-29.0)</td>
<td>22.6 (16.8-28.5)</td>
<td>0.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SSST (sec)\textsuperscript{b}</td>
<td>6.6 (5.6-7.6)</td>
<td>6.5 (5.4-7.6)</td>
<td>6.6 (5.6-7.7)</td>
<td>6.7 (5.6-7.7)</td>
<td>0.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EQ-5D-5L-Index value (0-1, au)\textsuperscript{b}</td>
<td>0.85 (0.78-0.91)</td>
<td>0.84 (0.78-0.91)</td>
<td>0.84 (0.78-0.90)</td>
<td>0.81 (0.76-0.86)</td>
<td>0.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EQ-5D-5L-VAS (%)\textsuperscript{c}</td>
<td>85.0 (65.0-95.0)</td>
<td>82.0 (65.0-95.0)</td>
<td>90.0 (75.0-95.0)</td>
<td>85.0 (80.0-95.0)</td>
<td>0.07</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Values after 12 weeks of treatment.
\textsuperscript{b}Mean (95% CI)
\textsuperscript{c}Median (IQR)
\textsuperscript{d}End-values after 24 weeks of treatment were compared with paired statistics. For normalized isometric strength, values from all visits were compared using paired ANOVA.
Assessed for eligibility (n=38)

Excluded (n=18)
- Not meeting inclusion criteria (n=11)
- Declined to participate (n=7)

Randomized (n=20)

fSCIG
Allocated to intervention (n=10)
- Received allocated intervention (n=10)

Discontinued intervention (n=1)
- Potential side-effects

Analysed (n=9)
- Excluded from analysis (n=1)
  - No measurements obtained at any therapy


cSCIG
Allocated to intervention (n=10)
- Received allocated intervention (n=10)

Discontinued intervention (n=0)

Analysed (n=10)