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Review Article

Subcutaneous immunoglobulin treatment in CIDP and MMN. *Efficacy, treatment satisfaction and costs*

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ABSTRACT

Subcutaneous administration of immunoglobulin (SCIG) in chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) has been reported in several case reports and in a few randomized trials during the last decade. In this review we present the studies on SCIG in CIDP and MMN with special focus on the clinical effects. Moreover, the effect on quality of life, side effects to SCIG and the health economic perspectives are reviewed. Nine case studies, three randomized trials and six long-term, follow-up studies were identified. Most of the studies are conducted in patients switched from regular IVIG to SCIG treatment; one study involves treatment-naïve patients. The review shows that none of the studies have been powered to demonstrate an effect on disability. SCIG can maintain muscle strength for a period of 1 to 2 years and ability seems preserved for a similar period. Quality of life is generally unchanged or improved after switch to SCIG and generalized side-effects seem fewer, whereas local reactions at the injection site occur. Health economic analyses favour SCIG at the doses used in the reviewed studies.

Contents

1. Introduction

Intravenous infusion of immunoglobulins (IVIG) is a well-established therapy for the chronic immune-mediated neuropathies Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN) [1,2]. There are several reports on the effect of subcutaneous infusion of immunoglobulins (SCIG) in CIDP and MMN. Small, controlled and randomized studies document the short-term effect and open-labelled follow-up studies document the long-term effects. This review reports the present status of SCIG therapy in CIDP and MMN.

1.1. Preparations of immunoglobulin for subcutaneous infusion and their chemistry

The immunoglobulin products used for intravenous infusion are available at 5 or 10% concentrations. Two 10% immunoglobulin products for intravenous use can also be given subcutaneously, Gammard Liquid

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(Shire) and Gamimune® (Cutter Biological). Five immunoglobulin products for subcutaneous administration registered in Europe and North America are all produced at higher concentrations, thereby reducing the volume and infusion time; the five products are Subcuvia® (Shire) 16%, Gammanorm® (Octapharma) 16.5%, Hizentra® (CSL Behring) 20% and Cuvitru (Shire) 20%.

Each product has different preparation techniques. Gammanorm® and Subcuvia® are comparable with respect to excipients, concentration and storage. Subcuvia®, Gammanorm® and Cuvitru® glycine is used as excipients, whereas L-proline is used for Hizentra®. Content of the various IgG subclasses is almost identical for the four preparations varying between 50 and 75% for IgG1, 20 and 45% for IgG2, 2 and 10% for IgG3 and 0.5 and 5% for IgG4. The IgA content is comparable for Hizentra®, Cuvitru® and Gammanorm® the amount being 50 and 82.5 μg per mL, whereas Subcuvia® has a higher content of 4800 μg/mL [3–6].

All subcutaneous preparations are recommended to be stored at temperatures below 8° C. Hizentra® can be stored for up to 36 months at room temperature, whereas Gammanorm®, Subcuvia® and Cuvitru® can be stored at room temperature for 1, 3 and 12 months, respectively. There is no evidence concerning efficacy of the three preparations. It is possible that tolerability of the various products differs among patients, but data to support this are sparse.

1.2. Pharmacokinetics of SCIG infusion in relation to dosage and treatment interval

Intravenous and subcutaneous infusions of immunoglobulins have different pharmacokinetics and dynamics. Studies in patients with primary immune deficiencies (PID) have shown that the bioavailability of SCIG measured in serum is only 65–70% of that of IVIG [7]. Moreover, when immunoglobulin is administered subcutaneously the majority is absorbed in the lymphatic vessels and transported into the blood stream [8], only a smaller fraction reaching it. Following subcutaneous infusion, arrival of IgG into the blood stream is, therefore, delayed and the peaks of IgG are lower compared with intravenous infusion. This might contribute to reduce occurrence of side-effects in patients switching from IVIG to SCIG treatment [7,9].

In PID, the therapeutic aim is to reach a threshold level of plasma immunoglobulin to avoid infections. In CIDP and MMN, a correlation between plasma IgG (P-IgG) levels and motor performance has not been established [10]. Nevertheless, in a study of Guillain-Barré syndrome, Kuitwaard et al. showed that the delta value of P-IgG at start of and two weeks after IVIG infusion of 2 g/kg bodyweight (bw) was related to the clinical outcome [11].

The most frequently used procedure at switch from IVIG to SCIG is the maintenance of an equivalent dose of 1:1. Some patients subsequently increase their dosage, indicating the switch to SCIG at a 1:1 dose is suboptimal. Based on pharmacokinetic studies on the area under the curve (AUC), the FDA required a dose adjustment coefficient (DAC) of 1.20 to 1.53 for a switch from IVIG to SCIG in patients with PID [7]. This approach is not used in Europe, and a study by Katzberg et al. using a switch at a dosage of 1:1.53 showed no further benefit in patients with MMN than described in studies using a 1:1 equivalent switch. Nevertheless, three out of six patients in whom an equivalent dose was applied experienced a clinical deterioration [12]. A possible explanation for a similar effect of a 1:1 dosage despite lower bioavailability might be more favorable pharmacokinetics obtained following multiple small doses of SCIG with more stable levels of P-IgG compared to a few large infusions of IVIG.

One of the first studies of SCIG in patients with MMN showed that a 50% dose-reduction compared to IVIG led to treatment failure [13]. Afterwards, in two 24-month follow-up studies demonstrated dose increments of 21% in two thirds and 15% in one fourth of the patients. In CIDP, Markvardsen et al. observed that the dosage increased by 6.4% in almost half of the patients, whereas Cocito et al. reported a 20% increase in a minority of the patients. In the study by Hadden et al., CIDP patients had an average increase of approximately 8% after a follow-up period of 33 months [14–17].

Wear-off phenomena of muscle strength during regular IVIG therapy are well-recognized [18], but to our knowledge this has not been studied in SCIG therapy.

1.3. Side-effects following SCIG therapy

Studies and reports on side-effects after SCIG are few. Local reactions such as redness, itching and swelling at the injection site are common whereas systemic side-effects are rare. We performed an open-label, prospective study comparing severity of headache and nausea in 59 patients treated with IVIG for CIDP, MMN or a post-polio syndrome as well as in 26 patients treated with SCIG for CIDP or MMN. The participants assessed the severity of headache and nausea daily on a Visual Analogue Scale (VAS) for 14 days after an IVIG infusion or a defined period of 14 consecutive days during SCIG treatment. Headache and nausea were significantly reduced during SCIG compared to IVIG therapy. Furthermore, we found that 74% of the patients treated with SCIG did not experience headache at all; this was the case for 32% at the patients treated with IVIG. Concerning nausea, 74% of patients treated with SCIG were symptom free compared to 57% of those treated with IVIG [19].

The occurrence of hemolytic anemia following infusion of IVIG has been reported in groups of patients as an integral part of the treatment. This is seemingly due to higher levels of antibodies against the ABO blood type system in new liquid immunoglobulin preparations. Anemia following IVIG therapy is associated with the presence of anti-A and anti-B antibodies [20,21]. In a clinical prospective study we included 84 patients treated with IVIG and measured hemoglobin levels as well as parameters related to hemolysis before and 14 days after infusion. Overall, we found that hemoglobin levels were depleted and that the changes of hemolytic parameters including the reticulocyte count, bilirubin, haptoglobin and lactate dehydrogenase indicated mild hemolysis. Moreover, patients with blood type A, B or AB had lower levels of hemoglobin than those with blood type 0 [22]. Whether hemolysis is caused by the route of administration, high peak levels of immunoglobulin or antibodies against the AB0 system is unknown [23]. Interestingly, results from a recent study suggest that hemoglobin levels can be normalized following a switch from IVIG to SCIG [24], suggesting that route of administration plays a role.

1.4. Health economic consequences of subcutaneous immunoglobulin therapy

In PID, several studies have been conducted evaluating the cost effectiveness of switching patients from regular in-hopsital IVIG infusion to home-based SCIG treatment [25–27]. They all conclude that SCIG is the most cost-effective, as the costs for SCIG are lower due to the absence of professional supervision of the infusions. Moreover, the avoiding transportation to hospital as well as lost income during hospitalization further improves the cost-effectiveness of SCIG therapy. Although some patients might need increase of their immunoglobulin doses, SCIG therapy is still cost-effective using the reported increased doses.

In neurology, the cost-effectiveness of the SCIG regimen has been sparsely studied. Two small studies from Italy have addressed the impact of switching to SCIG in CIDP and MMN [28,29]. In a cost-minimization analysis of the direct costs of each treatment regimen, Cocito et al. estimated a 600€ annual saving on SCIG therapy not considering indirect costs [28]. Furthermore, Lazzaro et al. evaluated both direct and indirect costs of IVIG vs SCIG in CIDP and MMN and confirmed that according to a cost-minimization analysis, SCIG therapy is less expensive compared with IVIG therapy. The overall estimated savings amounted to 1300€ per patient per year [29].

To sum up, these findings suggest that subcutaneous administration is financially advantageous in neurological patients requiring

immunoglobulin treatment. However, various countries have different reimbursement rules and different expenses for immunoglobulins making it difficult to compare costs.

2. Effects of subcutaneous immunoglobulin on muscle strength and disability

The studies available for evaluation of the efficacy of SCIG treatment are not powered to show differences in disability scores. Thus, in our studies, isokinetic dynamometry, which is a reproducible, sensitive, and "objective" technique, was used for evaluation as the primary parameter. In most other studies a clinical semi-quatitative MRC sum score was applied.

A recent meta-analysis from 2016 comparing IVIG and SCIG included eight studies with 138 patients (50 MMN and 88 CIDP) and concluded that there is no significant difference in outcome for muscle strength neither in MMN nor in CIDP [30].

2.1. Chronic inflammatory demyelinating polyneuropathy

Eleven published studies include 188 SCIG treated patients with CIDP of whom 62 are represented more than once, resulting in 126 unique patients (Table 1).

The first case report from 2006 observed an improvement of the ODSS and MRC scores in a CIDP patient. The treatment was well tolerated; the dose was 0.1 g/kg/bw per week for six months [31]. The next case report from 2008 described two patients with CIDP treated for 5 and 13 years with IVIG and successfully switched to SCIG treatment and followed for 8 and 24 months, respectively. The treatment was well tolerated and the patients gained muscle strength and improved their disability [32]. In 2011, Cocito et al. reported on five patients with CIDP switched from IVIG to SCIG therapy for six months and evaluated with scores of MRC, disability (ONLS), Quality of Life (SF-36), grip strength and preferences concerning route of administration route of SCIG. No significant difference for any of the outcome parameters was observed. However, four of the five patients preferred SCIG treatment [33].

Finally, in 2013 Bayas et al. reported on two IVIG responders with multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) switched to SCIG and followed for 37 and 46 months. Both were stabilized during SCIG treatment according to their MRC and ODSS scores [34].

In 2013, Markvardsen et al. reported a randomized, double blind, placebo controlled parallel study on patients with CIDP on IVIG therapy complying with the EFNS/PNS criteria. All participants were treated for 12 weeks with placebo or SCIG at an equivalent 1:1 dose compared to their IVIG therapy. The primary outcome was the change in muscle strength of four pre-selected, and weakened muscle groups evaluated at isokinetic dynamometry (Biodex Pro System 3, Biodex, New York, USA) [35]. Secondary outcomes were changes of an overall disability sum score (ODSS), grip strength, a 40-meter walking test, a 9-hole-peg test and plasma IgG levels. Moreover, patients were asked about their preference of SCIG vs IVIG treatment. Isokinetic muscle strength increased by 5.5 ± 9.5% ($p < 0.01$) in the SCIG group compared to a deterioration of 14.4 ± 20.3% ($p < 0.01$) in the placebo group; difference between the groups was statistically significant ($p = 0.004$).

Table 1
Overview of the published clinical trials of SCIG in CIDP and MMN.

Study	N MMN	N CIDP	Design	Endpoint	Follow-up time (weeks)
Koller 2006 [31]	2	1	Case series,	INCAT disability, MRC	104
Lee 2008 [32]		2	Case series,	SSS, MRC, ODSS, NCS	32 to 104
Harbo 2009 [39]	9		Randomized, single-blind, placebo-controlled, cross-over IVIG vs SCIG	**Isokinetic and handgrip strength**, MRC, SF-36, 9-hole peg, 10 m walk, IgG, NCS, GM1-ab	7 to 16
Eftimov 2009 [13]	10		Prospective, open-label, 50% and 100% switching dose from IVIG	**MRC sum score**, grip strength, INCAT and AMC linear disability scale, 9-hole peg, SF-36, P-IgG.	26
Harbo 2010 [15]	6[a]		Prospective, open-label extension	**Isokinetic and handgrip strength**, INCAT overall disability sum score, Neuropathy Impairment score.	104
Dacci 2010 [41]	1		Case report	MRC sum score	141
Woodall 2010 [38]	3		Case series	Grip strength, 9-hole peg, duration of right heal raise	12 to 52
Misbah 2011 [40]	8		Prospective, case series	**MRC sum score,** Guy's disability score, HRQOL, LQI, motor performance daily activity scale, VAS global health, IgG	24
Cocito 2011 [33]		5	Case series	**MRC sum score, ONLS, grip strength**, SSS, SF36, LQI	26
Braine 2012 [42]	16 *7 SCIG 9 IVIG*		Cross-sectional study comparing SCIG and IVIG.	SF-36, LQI, TSQM, semi-structured interview	12 to 144
Markvardsen 2013 [10]		29 *14 SCIG* vs *15 placebo*	Randomized, double-blind, placebo controlled	**Isokinetic strength,** ODSS, grip strength, MRC, 9-hole peg, 40 m walk, IgG	12
Cocito 2013 [44]		10	Open label, SCIG 16% vs SCIG 20%	MRC, ONLS, SSS, LQI	12 + 12
Bayas 2013 [34]		2 (MADSAM)	Case series	MRC, ODSS	148 to 184
Markvardsen 2014 [14]		17[b]	Prospective, open-label extension study	**Isokinetic strength,** ODSS, grip strength, MRC, 9-hole peg, 40 m walk, IgG	52
Cocito 2014 [36]	21	66	Prospective, multicenter case series	**ONLS, MRC sum score**, Life Quality Index	16
Hadden 2015 [17]	4	4	Partially prospective case series	ONLS, MRC sum score, treatment satisfaction	78 to 224
Cocito 2015 [16]	21[c]	45[c]	Prospective, multicenter case-series	**Adherence to therapy,** ONLS, MRC sum score, Life Quality Index	104
Yoon 2015 [47]	1	3	Retrospective, case series	MRC sum score	52 (MMN)
Katzberg 2015 [12]	15		Prospective, case series,	MRC sum score, grip strength, Guy's upper limb disability, HUI-QOL, IgG	26
Markvardsen 2016 [37]		19	Randomized, single blind, cross-over	**Isokinetic muscle strength**, MRC, ODSS	10 + 10
Total n/n dual represented	108/26	188/62			

Predefined primary outcome is highlighted in bold writing.
[a] 5 from previous study, 1 extra.
[b] 17 from previous study.
[c] 21 MMN and 45 CIDP from previous study.

Moreover, it was demonstrated that the ODSS score was significantly higher in the SCIG group than in placebo group with an improvement of 0.4 ± 0.7 points in the former group and a decrease of 0.7 ± 1.5 points in the latter group ($p = 0.04$). Among the other secondary endpoints we found a beneficial effect of SCIG on the MRC score, grip strength and 40-meter-walking test compared to the placebo group. In the SCIG group, P-IgG was maintained at a level of 18.4 ± 5.2 g/L at the end of study compared to 11.3 ± 2.7 g/L in the placebo group. No correlation between P-IgG levels and change of isokinetic muscle strength was demonstrated ($r^2 = 0.02$, $p = 0.24$, $n = 58$) [10].

In 2014, Markvardsen et al. reported on 17 patients on SCIG treatment followed for 12 months after participation in their RCT study [10]. Muscle strength increased by 7.2% ($p = 0.033$) during the 12 months follow-up with non-significant improvements after 3, 6 and 12 months of 5.7%, 8.2% and 6.8%, respectively. None of the patients experienced a deterioration of isokinetic muscle strength of >15%. The average dose of SCIG was increased by 20% during the 12 months follow-up [14].

In a nationwide Italian, multi-center, prospective study of 66 IVIG-treated patients with CIDP switched from monthly IVIG to weekly SCIG. Primary endpoints were changes on an overall neuropathy limitation score (ONLS) and a MRC sum score (MRC). ONLS improved from 4.1 ± 2.8 to 3.1 ± 2.0 points whereas the MRC score was unchanged indicating that the SCIG group maintained muscle strength [36]. In a follow-up study on 45 of the patients with CIDP, the authors reported that the adherence to SCIG treatment decreased to 76% after 24 months and that the rate of clinical worsening in patients with CIDP was 13.3% [16].

Hadden et al. reported on the switch of four CIDP patients from regular IVIG to SCIG therapy and found that the clinical MRC score and disability was stable during 31 months of follow-up [17].

The first study to address the effect of SCIG in treatment-naïve, de-novo patients with CIDP was published recently. In this randomized and controlled, cross-over study, muscle strength improved by 10.7% two weeks after one IVIG infusion of 2 g/kg during five days compared to 11.2% after five weeks of SCIG (0.4 g/kg/week). The improvement associated with SCIG and IVIG infusions was similar, but the time profiles were different. After two weeks muscle strength improved in the IVIG arm, whereas strength improved after five weeks in the SCIG arm. As secondary endpoints grip strength, MRC score, walking test performance and disability were evaluated. All endpoints improved in both treatment groups except grip strength [37].

2.2. Multifocal motor neuropathy

In 13 identified studies, 108 SCIG-treated patients with MMN were included of whom 26 are represented twice resulting in 82 unique patients (Table 1).

In 2006, the first case reports were published suggesting that SCIG could be an alternative to IVIG for treatment of MMN [31]. A 64-year-old woman and a 73-year-old man on IVIG maintenance treatment for 2–3 years were switched to a corresponding 1:1 dosage of SCIG (0.1 g/kg/week). The woman stopped the treatment after nine weeks due to a generalized rash whereas the man remained stable on the ODSS and MRC score for six months. Three other patients with MMN [38] due to reported side-effects or treatment inconvenience were successfully switched to SCIG from IVIG.

One randomized, controlled study has been conducted, applying a non-inferiority, single-blind, cross-over design to compare the efficacy of SCIG and IVIG on motor performance in MMN. Only immunoglobulin responsive patients with at least a 10% decline in muscle strength measured at dynamometry at discontinuation of treatment were included. Nine patients were randomized to receive an equivalent dose of SCIG or IVIG for a period of three IVIG treatment intervals (mean of 84 days) and, subsequently, crossed over to the other treatment arm after wash out. The primary study parameter was isokinetic muscle strength in weakened muscle groups at wrist, elbow, shoulder, ankle, knee or shoulder or grip strength assessed by a hand-grip dynamometer. Secondary parameters were a MRC score, nerve conduction study, 9-hole-peg test, 10-meterwalking test, P-IgG, anti-GM1 as well as side effects. The median SCIG dose was 24.8 g/week (range: 15.2–24.8) administered twice or thrice a week. All patients completed the study having transient local side effects, only. Neither differences in motor performance nor any of the secondary parameters were found; thus, SCIG and IVIG treatment was equally effective [39].

Long-term data of an open label extension of the above-mentioned RCT study appeared in 2010. Five patients who preferred SCIG treatment at the end of the controlled trial and one additional patient were examined after 3, 6, 12 and 24 months. Their isokinetic muscle strength was stable with a median increase of 3.7% (range: −8.8 to 14.5). The ODSS and a standardized neurological examination score of manual muscle strength, reflexes and sensibility (Neuropathy Impairment Score) were unchanged. Only transient and mild local adverse effects were reported, without generalized symptoms. The median weekly initial dose of IgG was 25 g (range: 12.8 to 44.8). Four patients increased their dose by 20 to 25% during the study period [17].

Safety and muscle performance were assessed in a prospective, open-label study from the Netherlands. All patients had been stable on IVIG treatment for at least 6 months without changes of treatment within the last six weeks. In the original protocol it was hypothesized that a 50% reduction of the SCIG dose compared to the prior IVIG treatment would be effective. However, due to treatment failure in the first five included patients, a dose equivalent to the full IVIG dose was applied in the following five patients. In the adjusted treatment protocol, one patient deteriorated but was stabilized on a SCIG dose of 166% of the previous IVIG dose. The four patients completing the adjusted protocol at an IVIG equivalent dose had a stable MRC sum score during the six-month follow-up period at a mean monthly dose of 0.46 g/kg bw. All patients reported local adverse events, most frequently redness and swelling, with a decreasing incidence over time. Three patients reported mild systemic adverse events [13].

In 2011 Misbah and colleagues, in their case series on eight patients with MMN, established a smooth transition protocol where SCIG was initiated immediately after the last IVIG infusion at a weekly dose of 25% of the corresponding IVIG dose for the first week, gradually increasing to 50% in week two and to 100% in week three and further on. Before entering the study, patients had been treated in a hospital-based program with monthly IVIG of 1.0 g/kg (range: 0.44 to 1.9) for at least 12 weeks. The follow-up period was 24 weeks and the primary outcome was the MRC score. The most severely affected patient, failed to respond to SCIG and was excluded after 13 weeks and further two patients had a dose increase of 25% during the study. The non-responding patient had a decline in P-IgG from 18.9 to 9.35 g/L. The MRC sum score and disability score in the seven patients completing the study were unchanged from baseline to last follow-up. Edema and pruritis at injection-sites were reported as treatment related side effects [40].

After the study, one patient was followed for 141 months on SCIG treatment. After a dose adjustment to 125% of the IVIG dose, muscle strength stabilized on SCIG. At IVIG therapy this patient experienced end of dose weakening, suggesting that the dose was suboptimal before shifting to SCIG [41].

In a large Italian cohort of patients with inflammatory neuropathy, 21 subjects with MMN were followed for four months. Treatment was individualized and had been ongoing for at least six months prior to study. Continuing IVIG responsiveness was defined as a wear off effect before next infusion with a worsening of fatigue or an increase ≥1 on the ONLS or MRC sum score. SCIG was initiated 5–10 days after the last day of IVIG administered 1 to 3 times weekly at a (1:1) dose equivalent to the IVIG dosage. The patients treated with SCIG had unchanged ONLS and MRC sum scores. One patient, however, deteriorated two points on the ONLS score. A shift to the SCIG regimen was associated with fewer side effects. One patient had a painful erythema occurring

46 days after initiation of SCIG requiring return to IVIG for two courses after which SCIG was reinitiated without further complications. Expected transient local reactions were frequently seen. No need for dose increment was reported in this short-term study [36].

The same Italian cohort was followed for further two years, (27.9 ± 14.9 months) with adherence to therapy as the primary outcome. Four patients discontinued treatment because of worsening of their clinical condition. Furthermore, one patient required a 15% increase of the IgG dose after 24 months and four had an extra half IVIG infusion dose at 1 (two patients), 6 and 12 months after switch of therapy. The overall rate of clinical worsening, defined as a ≥ one-point increase at the ONLS scale, requiring an augmentation of the SCIG/IVIG dose or a return to IVIG therapy was 42.9%. No predictors of long-term adherence to therapy were observed among the baseline clinical characteristics of age, disease duration, IgG dose, ONLS or MRC sum score [16].

Hadden et al. included four patients meeting the EFNS/PNS criteria for MMN in a partially prospective observational study where IVIG therapy was switched at a 1:1 SCIG regimen. Patients who were stable on IVIG were consecutively enrolled, if they required <25 g IgG per week, if the treating neurologist found them suitable for SCIG therapy and if the patient was keen to switch. All patients obtained stable motor performance and unchanged disability. Adverse effects were mild with an overall high score on a treatment satisfaction index, all continuing SCIG after the study period [17].

Recently, a study group from Toronto published a series of 15 IVIG responsive patients with MMN s who were switched from an IVIG maintenance regimen to SCIG. As a novel approach, the SCIG dose was based on the previously established IVIG dose multiplied by a factor of 1.53. However, due to regulatory requirements of a maximal monthly dose of 2 g/kg, this protocol could only be applied in nine of the 15 patients. SCIG was initiated one week after an IVIG infusion using the smooth transition protocol as described by Misbah [40]. Eleven of the 15 included patients remained stable and completed the six-month study period. In the remaining group, three dropped out due to deterioration of muscle performance already at month three, and one experienced intolerable side effects with local swelling and elevation of liver enzymes. The three patients deteriorating during SCIG therapy were characterized by severe weakness with a MRC sum-score <35 and a grip strength <8 kg. Also, they already received the maximally allowed IgG dosage of 2 g/kg/month. Therefore, the 1.53 dose adjustment could not be made in these patients and their P-IgG levels decreased. Seven patients declined participation due to unwillingness to try new treatment, needle phobia or unability to self-inject SCIG. One had severe skin erythema and with increased liver enzymes and was excluded. The 1.53 adjustment dose was well tolerated, but without additional benefits [12].

3. Quality of life and patient satisfaction

Quality of life and treatment satisfaction most likely depend on the efficacy of immunoglobulin therapy. In addition, treatment related side-effects, discomforts and the settings in which the administration of immunoglobulin is provided play a role.

When comparing patient satisfaction and quality of life in IVIG and SCIG treatment, one should recognize that most available cases and studies are based on patients being switched from IVIG to SCIG leading to selection bias towards patients dissatisfied with their previous IVIG treatment. Randomized, controlled studies of previously untreated patients are thus needed to address this question.

Focusing on QoL and treatment satisfaction, Braine and Woodall in 2012 using quantitative as well as qualitative methods reported a small cross-sectional study including 16 patients treated with high-dose IgG for MMN. Nine received hospital-based IVIG treatment whereas seven had been switched to self-administered SCIG treatment 3 to 33 months earlier. A treatment Satisfactory Questionnaire for Medication (TSQM) was applied together with a 30-minute semi-structured interview. Treatment satisfaction evaluated using the questionnaire was overall higher in the SCIG group, especially at the subscale for side effects ($p = 0.01$). The interview focused on the differences between IVIG and SCIG. Gain of time, increased treatment flexibility, normalization of life condition, stabilization of treatment effect, reduced side effects, and an overall feeling of having self-control with their condition were the main themes reported following shift to SCIG therapy [42].

Similar results were found in a Dutch cohort of 10 patients with MMN switched from home care IVIG treatment to self-administered SCIG for half a year with no changes of the SF-36 summary score [13]. In the first the Italian multicenter study of CIDP and MMN, four patients out of five increased their physical component score (SF-36) [43] and three increased their mental component score after being switched from IVIG to SCIG [33]. Several other studies from the Italian group, including 87 CIDP and MMN patients aged 57 years (range: 12 to 84), have reported on various aspects of SCIG therapy including quality of life and treatment satisfaction [16,36]. In the Braine and Woodall study where a SF-36 questionnaire was applied in two groups of patients with MMN who had chosen to either remain on IVIG or switch to SCIG treatment, the SCIG group scored higher in all SF-36 domains, reaching statistical significance in the vitality dimension as well as in the mental component summary score [42].

Using a Life Quality Index (LQI), six of eight patients improved in the study [40], and Braine and Woodall found higher scores in SCIG-treated patients for all items except pain [42]. Cocito et al. found higher scores in all scales, numbers being statistical significant for the subscales indicating that SCIG improved the perception of the therapeutic setting and reduced the interference with activities of daily living [16,36]. Furthermore, in a small study, a higher LQI score was found when a higher SCIG concentration resulted in less frequent infusions [44]. In the Netherlands where IVIG treatment is offered in home-based settings, a relationship between SCIG and LQI could not be established [13]. In summary, available data indicate that self-administered SCIG treatment in CIDP and MMN leads to improved QOL and treatment satisfaction compared to in-hospital IVIG therapy.

4. Future studies on subcutaneous immunoglobulin therapy in CIDP and MMN

Large scale RCT studies on SCIG are needed to assess the effect in CIDP and MMN. An ongoing study conducted by CSL Behring assesses the effect of SCIG in CIDP (NCT01545076). Patients with CIDP undergo a test period of 12 weeks to ensure the response to immunoglobulin (IVIG re-stabilization phase) and are subsequentlyrandomized to receive either SCIG treatment with 0.2 or 0.4 g/kg BW per week or placebo for 24 weeks. The study plans to include 350 patients worldwide and was announced to run from March 2012 to September 2016. The primary outcome is the proportion of patients having a relapse during the subcutaneous treatment period, secondary outcomes being changes of an INCAT neuropathy score, grip strength, MRC, changes in R-ODS score and adverse events during SCIG treatment [45].

A new preparation of immunoglobulin for subcutaneous administration including pre-treatment with hyaluronidase, so-called facilitated SCIG (fSCIG), has been released for use in humans. It is feasible to infuse a maximum volume of 600 mL of immunoglobulin at one injection site. In patients with neurological diseases this could make administration of subcutaneous immunoglobulin more flexible with only one infusion every 1–4 weeks. A large commercial trial by Baxalta/Shire will evaluate the safety, efficacy and tolerability in patients with CIDP in a randomized, double-blind and placebo-controlled design including 232 patients. The primary outcome is the relapse and response rate to fSCIG. Secondary outcomes are time to relapse, disability changes evaluated as a R-ODS score and adverse events. The study started in November 2015 and closes in January 2019 [46].

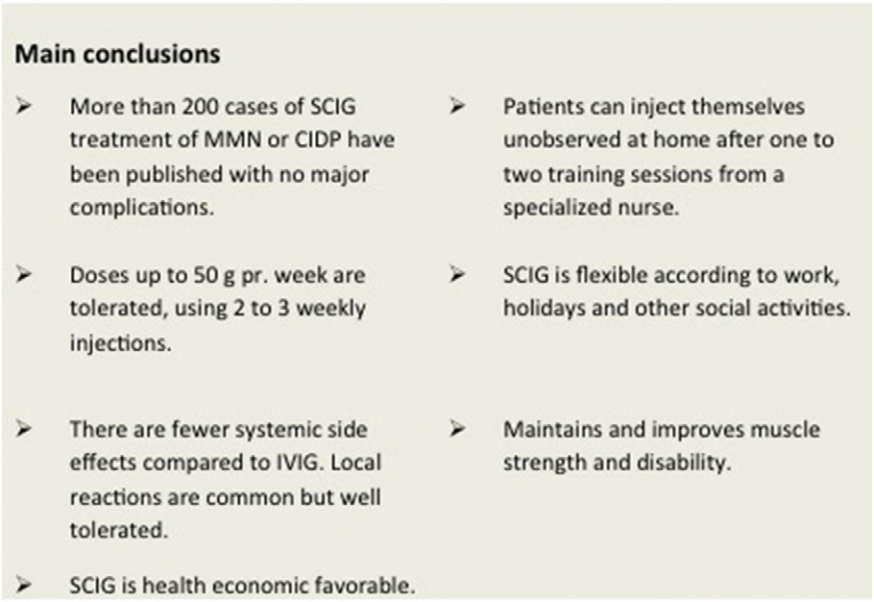

Fig. 1. Main conclusions of SCIG treatment in CIDP and MMN.

In patients with MNN, two small ongoing open-labelled studies in the Netherlands and Denmark evaluate the effect and feasibility of fSCIG therapy following switch from ongoing IVIG or SCIG therapy, respectively.

5. Conclusion

Case studies, small short-term randomized and controlled trials as well as open-labelled long-term observations all indicate that maintenance treatment with SCIG can preserve muscle strength in patients with CIDP and MMN. In additon, it seems that function and ability are maintained as well.

The optimal SCIG dosage might be slightly higher than the one used for IVIG therapy. A recently published study indicates that subcutaneous infusion of IgG can be applied initially in untreated de-novo patients with CIDP. In general, side-effects seem to be restricted to local reactions at the infusion site. Quality of life scores seem to improve when compared to intravenous infusion during hospitalization and the majority of patients switched to SCIG therapy prefer to continue their regimen. Studies of cost-effectiveness will vary between countries but favors SCIG infusion (Fig. 1).

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