

Intravenous Immunoglobulin Therapy in Patients With Painful Idiopathic Small Fiber Neuropathy

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Abstract

Objective

This is the first double-blind randomized controlled trial evaluating the efficacy and safety of IV immunoglobulin (IVIG) vs placebo in patients with idiopathic small fiber neuropathy (I-SFN).

Methods

Between July 2016 and November 2018, 60 Dutch patients with skin biopsy–proven I-SFN randomly received a starting dose of IVIG (2 g/kg body weight) or matching placebo (0.9% saline). Subsequently, 3 additional infusions of IVIG (1 g/kg) or placebo were administered at 3-week intervals. The primary outcome was a 1-point change in Pain Intensity Numerical Rating Scale score at 12 weeks compared to baseline.

Results

Thirty patients received IVIG, and 30 received placebo. In both groups, 29 patients completed the trial. In 40% of patients receiving IVIG, the mean average pain was decreased by at least 1 point compared to 30% of the patients receiving placebo ($p = 0.588$, odds ratio 1.56, 95% confidence interval 0.53–4.53). No significant differences were found on any of the other prespecified outcomes, including general well-being, autonomic symptoms, and overall functioning and disability.

Conclusions

This randomized controlled trial showed that IVIG treatment had no significant effect on pain in patients with painful I-SFN.

Trial Registration Information

ClinicalTrials.gov Identifier: NCT02637700, EudraCT 2015-002624-31.

Classification of Evidence

This study provides Class I evidence that for patients with painful I-SFN, IVIG did not significantly reduce pain compared to placebo.

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Glossary

DSIS = daily sleep interference scale; **I-SFN** = idiopathic SFN; **ITT** = intention-to-treat; **NPS** = Neuropathic Pain Scale; **PGIC** = patients' global impression of change; **PI-NRS** = Pain Intensity Numeric Rating Scale; **PP** = per-protocol; **RT-SFN-SIQ** = Rasch-transformed 13-item SFN Symptoms Inventory Questionnaire; **SAE** = serious adverse event; **SF-36** = Short Form 36 Health Survey; **SFN** = small fiber neuropathy; **SFN-RODS** = Rasch-transformed SFN Overall Disability Scale.

Patients with small fiber neuropathy (SFN) commonly complain of length-dependent neuropathic pain symptoms due to dysfunction and degeneration of thinly myelinated A δ and unmyelinated C fibers.^{1,2} Pain symptoms occur spontaneously (e.g., burning, deep, paroxysmal pain) and can be elicited by innocuous stimuli (e.g., light touch or pressure, warm and cold water). Different underlying systemic illnesses³⁻¹¹ and genetic diseases¹²⁻¹⁶ are associated with SFN. However, in 53%, an underlying etiology remains unknown (idiopathic SFN [I-SFN]). Immunologic mechanisms have been speculated to contribute to patients with I-SFN because several immune-mediated disorders such as sarcoidosis, Sjogren disease, and systemic lupus erythematosus have shown some association with SFN.^{3,7,17-19} In addition, autoantibodies have been seen in patients with SFN,²⁰⁻²³ inflammatory modifications in nerves have been noticed,^{24,25} raised proinflammatory cytokines potentially influence the pathophysiology of pain in SFN,²⁶ and peripheral and central glial-mediated neuroimmune activation has been reported in maintaining chronic pain.²⁷

IV immunoglobulin (IVIG) is a successful, commonly used treatment for chronic immune-mediated polyneuropathies such as chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy.²⁸⁻³⁰ Several open-label case series have reported IVIG to be efficacious in immune-mediated SFN,³¹⁻³⁷ and a recent retrospective study suggested IVIG as an effective treatment option for patients with SFN with autoimmune diseases or nonspecific blood test markers for autoimmunity.³⁸ As a consequence, patients are frequently treated with this highly expensive drug,³⁹ despite the lack of proven effectiveness for IVIG in I-SFN through controlled trials. We present the results of a double-blind randomized controlled trial evaluating the efficacy and safety of IVIG vs placebo in patients with I-SFN.

Methods

The IVIG in I-SFN study was a randomized, placebo-controlled, double-blind study. A complete report of the study design has been published earlier,⁴⁰ and the outline is given below.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was performed in accordance with the guidelines of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines. The study

protocol was approved by the local Medical Ethics Committee. All patients in this trial gave written informed consent. This trial is registered with ClinicalTrials.gov (NCT02637700) and EudraCT (2015-002624-31).

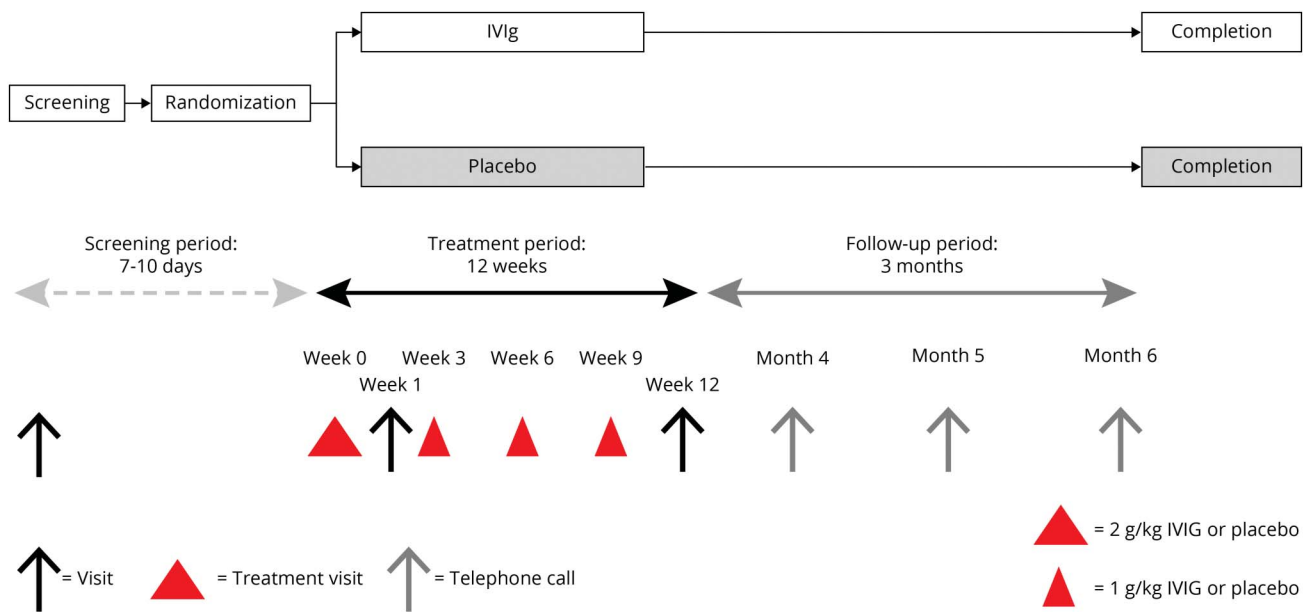
Study Design and Participants

All consecutive patients, not from a prevalent pool, were included and treated at the SFN Center at the Maastricht University Medical Center+, the Netherlands, between July 2016 and March 2019, after giving written informed consent. Patients with I-SFN were eligible after meeting the international diagnostic criteria of SFN (i.e., typical SFN-related symptoms described mainly as a burning sensation, shooting pains, prickling or itching, predominantly in a length-dependent pattern, with a minimum pain intensity score of ≥ 5 on the Pain Intensity Numeric Rating Scale [PI-NRS], combined with a reduced distal intraepidermal nerve fiber density in skin biopsy, excluding large fiber involvement) and without an underlying etiology (such as diabetes mellitus, *SCN9A/SCN10A/SCN11A* mutations, hypothyroidism, vitamin B₁₂ deficiency, Fabry disease, Sjogren syndrome, sarcoidosis, and celiac disease),^{1,2,15,41} which was routinely tested in all patients before study entry. Exclusion criteria included prominent non-length-dependent pattern, predominant clinical picture of large nerve fiber involvement (i.e., weakness, loss of vibration sense, hypoflexia/areflexia, abnormal nerve conduction studies of tibial, peroneal, and sural nerves, including distal latency, amplitude, and conduction velocity using surface electrodes with standard placement), receiving IVIG treatment or any other immunomodulatory/immunosuppressive agents (e.g., steroids) within the 12 weeks before screening, and cardiac insufficiency (New York Heart Association class III/IV), cardiomyopathy, or significant cardiac dysrhythmia. The use of pain medication was allowed and registered if this remained stable in the 30 days before randomization. A change in dosage of (analgesic/antineuropathic) pain medication was not allowed throughout the study. Permissible medications were acetaminophen and nonsteroidal anti-inflammatory drugs such as ibuprofen, which were allowed during the trial as premedications for study drug infusions. A complete report of the inclusion and exclusion criteria was published previously.⁴⁰

Randomization and Masking

Patients were randomly allocated in 2 groups (IVIG or placebo) using the ALEA randomization software, provided by FormsVision BV (Abcoude, the Netherlands) with the minimization technique. Patients were stratified according to age and sex. All participants, care providers, and study personnel, including those assessing outcomes, except for those in the

Figure 1 Schematic Diagram Representing Overall Study Design and Study Visits



Red triangles represent the treatment visits. The first uploading treatment period was spread out over 2 consecutive days. The other treatment visits consisted of 1 day. IVig = IV immunoglobulin.

pharmacy, were blinded for treatment assignment. IVIG and matching placebo were provided in ethylene vinyl acetate infusion bags with masking covers for IV administration. For optimal masking, orange infusion lines (B. Braun Cyto-Set Infusomat Space PZN10759513) were used. The blinding codes were intact during the complete study.

Study Medication and Procedures

The study medication was Gamunex (Grifols USA, LLC, Los Angeles, CA) 10%, 100 mg/mL solution for infusion of human normal immunoglobulin. Placebo was supplied as 0.9% saline. Figure 1 presents the study algorithm.⁴⁰ The study started with a screening period (maximum 10 days). Eligible individuals subsequently entered the study treatment period (duration 12 weeks) and were randomized to conceive either IVIG with an uploading dose of 2 g/kg body weight or placebo over 2 serial days, with a maximum dose of 80 g IVIG per infusion day. In addition, 3 infusions with a dose of 1 g/kg body weight were dispensed with a 3-week interval. This regimen was chosen as previously applied in patients with chronic inflammatory demyelinating polyneuropathy for evaluating the IVIG efficacy.²⁸ A final visit took place for all patients 3 weeks after the last infusion or after withdrawal for any reason during this period. After treatment completion, there was a 3-month-extension follow-up phase evaluating the possible long-term effect of IVIG on pain if any.

Trial Outcomes

The primary research question of this study was as follows: does IVIG significantly reduces pain compared to placebo for patients with painful I-SFN (Class I evidence)?

The primary efficacy outcome was the proportion of patients after the treatment period having at least a 1-point improvement on the 11-point PI-NRS (0 = no pain, 10 = worst imaginable pain) of their average pain compared to baseline, which is considered the minimum clinically important difference, according to unified rule of 0.5 SD and the guidelines.^{42,43} Patients also completed a daily sleep interference scale (DSIS) (11-point numerical scale; 0 = pain does not interfere with sleep, 10 = pain completely interferes with sleep).⁴⁴ Participants completed the PI-NRS and the DSIS 2 times per week in the morning and evening at scheduled time points. Additional questionnaires (patients' global impression of change [PGIC],^{42,43} the Rasch-transformed 13-item SFN Symptoms Inventory Questionnaire [RT-SFN-SIQ],⁴⁵ the Neuropathic Pain Scale [NPS],⁴⁶ the Short Form 36 Health Survey [SF-36], and the Rasch-transformed SFN Overall Disability Scale [SFN-RODS],⁴⁵ and the amount of pain relief [on a 5-point Likert scale])⁴⁷ were completed at each visit during the treatment period, during the telephone calls, and at the final follow-up visit. In addition, all pharmacologic pain treatments and pain-relieving activities were recorded. Safety evaluation characteristics included adverse events, laboratory tests, and vital signs.

Secondary efficacy outcomes were the proportion of patients having ≥ 2 -point average pain improvement compared to their baseline PI-NRS scores and changes in the mean, maximum, and average scores on the PI-NRS, NPS, DSIS, PGIC, Pain Relief, RT-SFN-SIQ, SFN-RODS, and SF-36.

Statistical Analyses

The sample size of 24 participants per group was determined with an assumed response rate of 25% in the placebo group and 60% in the IVIG group, a 1-sided α of 5%, and 80% power between the 2 groups (χ^2 test), including the assumption of a dropout rate of 20% (6 patients). Therefore, the aim was to include in total 60 patients in the study. An independent statistician (S.M.J.v.K.) analyzed the results according to the intention-to-treat (ITT) protocol.⁴⁰ For the primary ITT analysis for success, missing values were included as no success. Participants were analyzed for efficacy according to randomized treatment. For all questionnaires, the difference between baseline (screening period) and the end of the treatment period (outcomes of the 12th week) was calculated. To determine the baseline scores, all available data before randomization were taken. No data imputation was performed for missing observations. For the primary outcome, the proportion of patients with a decrease of at least 1 point was compared between the IVIG and placebo groups with a χ^2 test. In addition, the proportion of ≥ 2 -point decrease was compared. When the PI-NRS score after 12 weeks was missing (because of dropout or missing diaries), patients were labeled as nonresponders.

The differences in DSIS, NPS, and SF-36 scores between baseline and 12 weeks of treatment were compared between the 2 groups. For these continuous outcome measures, the *t* test was used. For the PGIC, the proportion of patients who were (very) much improved was compared to the proportion of patients with little or no improvement. For the RT-SFN-SIQ and SFN-RODS, the proportions of patients with

significant deterioration, significant improvement, and no significant change were calculated and compared between the IVIG and placebo groups according to the distribution-based minimum clinically important difference–standard error method, with a meaningful change with a score ≥ 1.96 standard error.⁴⁸ For pain relief, the proportion of patients with no/slight relief was compared with the proportion of patients with moderate/good/complete relief. The χ^2 test, or Fisher exact test when needed, was used to calculate the differences between the 2 treatment groups.

All the above-mentioned tests were repeated in the per-protocol (PP) analysis. Patients were included in the PP analysis if they had an available PI-NRS score at baseline and a 12-week postbaseline mean weekly pain PI-NRS score.

During the trial, the protocol was amended once to add a follow-up period, to remove the PGIC and Pain Relief questionnaires from the screening visit, to adjust the visit window, to add questions to patients' pain diary, and to adjust the infusion rates according to the protocol of the hospital.

Data Availability

Anonymized data not published in the article will be shared by request.

Results

Patients

After a thorough investigation, 64 patients met the inclusion and exclusion criteria, as shown in figure 2. These patients were screened and gave informed consent for participating in the IVIG-SFN study. Four patients (6.3%) were excluded due to anemia, abnormal EMG, vitamin B₁₂ deficiency, and glucose intolerance (all n = 1).

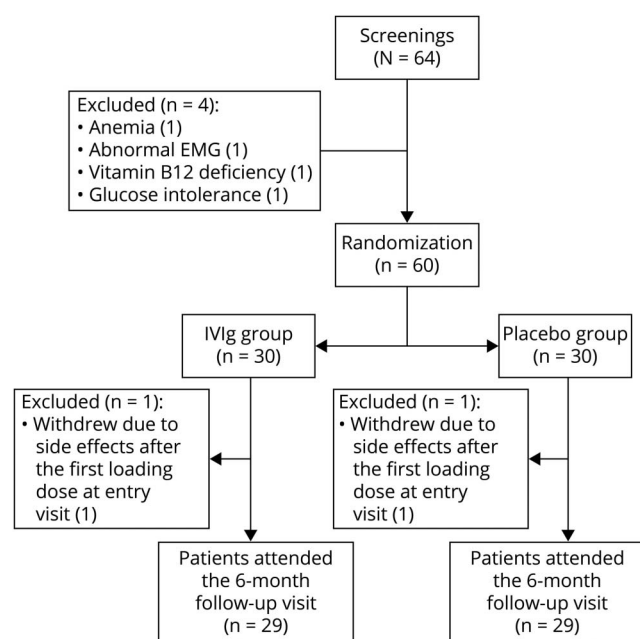
Sixty patients were randomized, 30 patients (50%) to IVIG and 30 to the placebo arm. Two patients (3.33%) withdrew their participation due to side effects (nausea, anxiety, fatigue, headache, and diarrhea) after the first uploading study medication dose at entry visit (1 patient was randomized to the IVIG arm, the other to placebo). Ultimately, 29 patients who received IVIG and 29 patients who received placebo completed the study.

All 60 patients were randomly assigned to received IVIG or placebo, and 294 of the 300 scheduled volumes (>95%) were actually dispensed. Patients endured a maximum volume of 240 mL/h of the uploading dose and a maximal volume of 560 mL/h for the additional infusions. Infusion time for the uploading dose was ≈ 5 hours and for the additional infusions 3 hours.

Baseline Characteristics

Baseline characteristics are shown in table 1. Patients in the 2 groups were similar in demographic, clinical, and disease-

Figure 2 Flowchart of the Trial



IVig = IV immunoglobulin.

Table 1 Baseline Characteristics of the Patients

	IVIG (n = 30)	Placebo (n = 30)
Age (at inclusion), mean (SD), y	48.7 (11.1)	50.7 (9.7)
Male, n (%)	10 (33.3)	12 (40.0)
BMI, mean (SD), kg/m ²	29.1 (5.0)	27.7 (5.1)
Duration of complaints SFN, median (range), y	7.8 (1.3–58.5)	7.4 (1.7–34.9)
White, n (%)	28 (93.3)	29 (96.7)
Presence of comorbidity, n (%)		
Hypertension	6 (20.0)	4 (13.3)
Hypercholesterolemia	7 (23.3)	5 (16.7)
Cardiac history	1 (3.3)	1 (3.3)
Age at skin biopsy/diagnosis, mean (SD), y	45.7 (9.8)	48.3 (10.7)
IENFD, mean (SD) ^a	3.2 (1.7)	3.1 (1.5)
TTT abnormal, n (%)	20 (66.7)	25 (83.3)
Diagnosis based on, n (%)		
Abnormal skin biopsy	10 (33.3)	5 (16.7)
Abnormal skin biopsy and TTT deviation	20 (66.7%)	25 (83.3)
Presence of typical SFN symptoms, n (%)		
Burning feet	27 (90.0)	26 (86.7)
Allodynia	22 (73.3)	20 (66.7)
Diminished pain or temperature sensation	21 (70.0)	21 (70.0)
Dry eyes or mouth	26 (86.7)	26 (86.7)
Orthostatic dizziness	21 (70.0)	12 (40.0)
Bowel disturbances	19 (63.3)	22 (73.3)
Urinary disturbances	18 (60.0)	18 (60.0)
Sweat changes	20 (66.7)	24 (80.0)
Visual accommodation problems or blurred vision	19 (63.3)	17 (56.7)
Hot flashes/palpitations	21 (70.0)	16 (53.3)
Impotence, diminished ejaculation or lubrication	11 (36.7)	13 (43.3)
Total typical SFN symptoms, median (range), n	8 (2–11)	7 (3–11)
IgG before treatment, mean (SD)	13.1 (9.6)	9.5 (2.2)
Use of (neuropathic) pain medication, n (%)		
Analgesics		
Acetaminophen	13 (43.3)	8 (26.7)
NSAID		
Ibuprofen	5 (16.7)	3 (10.0)
Diclofenac	2 (6.7)	2 (6.7)

Table 1 Baseline Characteristics of the Patients (continued)

	IVIG (n = 30)	Placebo (n = 30)
TCA		
Amitriptyline	1 (3.3)	3 (10.0)
Nortriptyline	1 (3.3)	1 (3.3)
SNRI		
Duloxetine	5 (16.7)	5 (16.7)
Anticonvulsant		
Gabapentin	5 (16.7)	1 (3.3)
Pregabalin	3 (10.0)	3 (10.0)
Carbamazepin	1 (3.3)	1 (3.3)
Opioids		
Oxycodone	4 (13.3)	1 (3.3)
Tramadol	2 (6.7)	1 (3.3)
Local anesthetics		
Capsaicin creme	0 (0.0)	1 (3.3)

Abbreviations: BMI = body mass index; IENFD = intraepidermal nerve fiber density; IgG = immunoglobulin G; IVIG = IV immunoglobulins; NSAID = nonsteroidal anti-inflammatory drugs; SFN = small fiber neuropathy; SNRI = selective serotonin and noradrenalin reuptake inhibitor; TCA = tricyclic antidepressants; TTT = temperature threshold testing.

^a Collected at the distal side of the right leg, 10 cm above the lateral malleolus; all patients had an abnormal IENFD (value below the fifth percentile of normal).

related characteristics at baseline. The baseline scores of the questionnaires are provided in table 2. For the ITT analyses, all 60 patients were used, and for the PP analysis, 10 patients were excluded (50 used; 24 in the IVIG group and 26 in the placebo group).

Primary Outcome

The primary outcome of the mean average pain scores based on the PI-NRS before and after treatment are shown in table 3: 40% of patients receiving IVIG and 30% of patients receiving placebo had at least a 1-point improvement in the average pain ($p = 0.588$, odds ratio 1.56, 95% confidence interval 0.53–4.53). The PP analysis and the 2-point decrease on the PI-NRS (ITT and PP analysis) also showed no significant differences.

Secondary Outcomes

Only a few of the secondary outcomes showed significant differences after 24 weeks (PI-NRS maximum night pain after 24 weeks $p = 0.029$, DSIS $p = 0.010$, NPS intense pain $p = 0.118$, NPS hot pain $p = 0.031$). SF-36 health change showed a significant difference after 12 weeks ($p = 0.007$); however, most secondary outcomes showed no significant difference between the effect of IVIG and the effect of placebo (table 3).

Table 2 Baseline Scores of Patients

	IVIG (n = 30)	Placebo (n = 30)	Total (n = 60)
PI-NRS score, median (range)			
Mean day pain	5.6 (3.0–8.3)	6.6 (2.3–9.5)	6.0 (2.3–9.5)
Mean night pain	5.8 (1.0–8.5)	5.4 (0.0–9.5)	5.7 (0.0–9.5)
Mean average pain	5.5 (2.0–8.3)	5.8 (1.7–9.5)	5.8 (1.7–9.5)
Maximum day pain	7.0 (3.7–10.0)	7.8 (3.3–10.0)	7.2 (3.3–10.0)
Maximum night pain	7.2 (1.5–9.5)	6.4 (0.0–10.0)	7.0 (0.0–10.0)
Maximum average pain	7.0 (3.0–9.8)	7.0 (2.2–10.0)	7.0 (2.2–10.0)
DSIS score, median (range)	5.5 (1.0–8.7)	5.8 (0.0–9.0)	5.5 (0.0–9.0)
SFN-SIQ score, median (range)	17.5 (6.0–35.0)	17.0 (6.0–35.0)	17.0 (6.0–35.0)
SFN-RODS score, median (range)	45.0 (27.0–64.0)	50.5 (31.0–64.0)	49.0 (27.0–64.0)
NPS score, median (range)			
Intense	7.0 (4.0–10.0)	7.0 (2.0–10.0)	7.0 (2.0–10.0)
Sharp	8.0 (0.0–10.0)	7.0 (0.0–10.0)	7.5 (0.0–10.0)
Hot	7.5 (0.0–10.0)	7.0 (0.0–9.0)	7.0 (0.0–10.0)
Dull	5.0 (0.0–10.0)	4.5 (0.0–9.0)	5.0 (0.0–10.0)
Cold	5.0 (0.0–9.0)	5.0 (0.0–10.0)	5.0 (0.0–10.0)
Sensitive	5.5 (0.0–10.0)	6.0 (0.0–10.0)	6.0 (0.0–10.0)
Itchy	1.5 (0.0–10.0)	5.0 (0.0–9.0)	4.0 (0.0–10.0)
Unpleasant	7.5 (4.0–10.0)	7.0 (3.0–10.0)	7.0 (3.0–10.0)
Intense deep	8.0 (1.0–10.0)	8.0 (0.0–10.0)	8.0 (0.0–10.0)
Intense surface	6.0 (2.0–9.0)	6.0 (2.0–10.0)	6.0 (2.0–10.0)
SF-36 score, median (range)			
Physical Functioning	50.0 (0.0–100.0)	50.0 (15.0–95.0)	50.0 (0.0–100.0)
Social Functioning	50.0 (0.0–100.0)	50.0 (0.0–100.0)	50.0 (0.0–100.0)
Role–Physical	28.1 (0.0–87.5)	28.1 (0.0–81.3)	28.1 (0.0–87.5)
Role–Emotional	83.3 (0.0–100.0)	75.0 (8.3–100.0)	79.2 (0.0–100.0)
Mental Health	75.0 (25.0–100.0)	70.0 (25.0–100.0)	75.0 (25.0–100.0)
Vitality	37.5 (0.0–93.8)	37.5 (6.3–81.3)	37.5 (0.0–93.8)
Bodily Pain	32.7 (0.0–79.6)	35.7 (10.2–69.4)	33.7 (0.0–79.6)
General Health	35.0 (5.0–75.0)	27.5 (0.0–90.0)	32.5 (0.0–90.0)
Health change	25.0 (0.0–75.0)	25.0 (0.0–100.0)	25.0 (0.0–100.0)

Abbreviations: DSIS = daily sleep interference scale; IVIG = IV immunoglobulin; NPS = Neuropathic Pain Scale; PI-NRS = Pain Intensity Numerical Rating Scale; SF-36 = generic Short-Form 36 Health Survey; SFN-RODS = Rasch-transformed Small Fiber Neuropathy Overall Disability Scale; SFN-SIQ = Small Fiber Neuropathy Symptoms Inventory Questionnaire.

After 12 weeks, 7 (24.1%) patients in the IVIG group and 4 (13.8%) in the placebo group were much or very much improved according to the PGIC ($p = 0.505$), and after 24 weeks, 4 (13.8%) patients in the IVIG group vs 3 (11.1%) in the placebo group ($p = 1.000$) were much or very much

improved. The PP analysis showed similar results. In addition, no differences were found in autonomic symptoms, overall disability, and pain relief; the RT-SFN-SIQ, SFN-RODS, and Pain Relief questionnaires, respectively, showed no significant differences between the 2 groups.

Table 3 Primary and Secondary Outcomes

Primary outcome	ITT		p Value	PP		p Value
	Proportion of responders, IVIG vs placebo (baseline vs 3 mo)			Proportion of responders, IVIG vs placebo (baseline vs 3 mo)		
≥1-Point decrease in average pain, n (%)	12 (40) vs 9 (30) OR 1.56 (95% CI 0.54–4.63)		0.588	12 (50) vs 9 (34.6) OR 1.89 (95% CI 0.61–6.04)		0.415
≥2-Point decrease in average pain, n (%)	7 (23.35) vs 5 (16.7) OR 1.52 (95% CI 0.43–5.78)		0.747	7 (29.2) vs 5 (19.2) OR 1.73 (95% CI 0.47–6.79)		0.624

Secondary outcomes	ITT				PP			
	Difference, baseline vs 3 mo, IVIG vs placebo	p Value	Difference, baseline vs 6 mo, IVIG vs placebo	p Value	Difference, baseline vs 3 mo, IVIG vs placebo	p Value	Difference, baseline vs 6 mo, IVIG vs placebo	p Value
Continuous outcomes								
PI-NRS score, mean (SEM)								
Mean day pain	-0.82 (0.41) vs -0.84 (0.38)	0.973	-0.72 (0.26) vs -0.46 (0.26)	0.474	-0.82 (0.41) vs -0.84 (0.38)	0.973	-0.82 (0.27) vs -0.51 (0.28)	0.431
Mean night pain	-1.23 (0.54) vs -0.28 (0.45)	0.185	-1.08 (0.45) vs 0.07 (0.33)	0.046	-1.23 (0.54) vs -0.28 (0.45)	0.185	-1.16 (0.49) vs -0.05 (0.37)	0.075
Mean average pain	-0.89 (0.38) vs -0.51 (0.36)	0.472	-0.90 (0.28) vs -0.19 (0.25)	0.067	-0.89 (0.38) vs -0.51 (0.36)	0.472	-0.99 (0.30) vs -0.28 (0.28)	0.086
DSIS score, mean (SEM)	-1.57 (0.51) vs -0.18 (0.44)	0.045	-1.17 (0.38) vs -0.43 (0.27)	0.010	-1.57 (0.51) vs -0.18 (0.44)	0.045	-1.64 (0.53) vs 0.51 (0.53)	0.006
NPS score, mean (SEM)								
Intense	-1.9 (0.47) vs -0.7 (0.29)	0.033	-1.72 (0.38) vs -0.43 (0.27)	0.118	-2.33 (0.50) vs -0.77 (0.30)	0.011	-0.46 (0.41) vs -0.56 (0.26)	0.073
Sharp	-1.4 (0.62) vs -0.6 (0.43)	0.260	-0.31 (0.57) vs -0.46 (0.37)	0.821	-1.92 (0.71) vs -0.46 (0.44)	0.089	-0.75 (0.63) vs -0.56 (0.38)	0.797
Hot	-1.6 (0.55) vs 0.2 (0.44)	0.017	-1.38 (0.51) vs 0.18 (0.48)	0.031	-1.75 (0.63) vs 0.15 (0.48)	0.021	-1.29 (0.58) vs 0.20 (0.52)	0.062
Dull	-1.8 (0.70) vs -0.8 (0.62)	0.273	-1.07 (0.84) vs 0.14 (0.57)	0.237	-1.50 (0.80) vs -0.96 (0.67)	0.608	-0.63 (0.95) vs 0.16 (0.59)	0.488
Cold	-1.4 (0.62) vs -0.7 (0.53)	0.354	-1.86 (0.66) vs -0.18 (0.64)	0.072	-1.58 (0.57) vs -0.46 (0.50)	0.146	-1.83 (0.61) vs -0.28 (0.63)	0.085
Sensitive	-1.9 (0.53) vs -0.9 (0.38)	0.108	-0.28 (0.53) vs -0.64 (0.47)	0.608	-1.96 (0.63) vs -0.73 (0.39)	0.107	-0.29 (0.64) vs -0.60 (0.51)	0.708
Itchy	-0.6 (0.39) vs -1.0 (0.61)	0.604	-0.48 (0.51) vs -0.61 (0.55)	0.868	-0.75 (0.42) vs -1.15 (0.57)	0.573	-0.46 (0.51) vs -0.76 (0.50)	0.674
Unpleasant	-1.7 (0.48) vs -0.6 (0.31)	0.052	-0.93 (0.42) vs -0.46 (0.34)	0.392	-2.08 (0.51) vs -0.62 (0.34)	0.022	-1.25 (0.39) vs -0.44 (0.37)	0.142
Intense deep	-1.5 (0.48) vs -1.6 (0.57)	0.889	-0.76 (0.38) vs -0.39 (0.50)	0.565	-1.75 (0.55) vs -1.27 (0.58)	0.548	-0.88 (0.44) vs -0.16 (0.53)	0.307
Intense surface	-0.9 (0.52) vs -0.3 (0.44)	0.365	-0.86 (0.49) vs 0.25 (0.44)	0.097	-1.42 (0.54) vs -0.69 (0.42)	0.295	-1.22 (0.52) vs -0.12 (0.41)	0.106
SF-36 score, mean (SEM)								
Physical Functioning	8.4 (3.55) vs 1.2 (2.23)	0.090	4.5 (4.61) vs 2.9 (3.07)	0.773	12.3 (3.81) vs 2.11 (2.27)	0.027	10.22 (4.28) vs 4.60 (3.13)	0.296
Social Functioning	5.6 (4.41) vs 6.9 (3.60)	0.821	4.5 (5.58) vs 1.3 (4.13)	0.655	8.90 (4.76) vs 6.25 (3.81)	0.553	9.24 (5.84) vs 1.50 (4.64)	0.305
Role-Physical	13.6 (4.09) vs 0.6 (3.83)	0.025	6.5 (4.45) vs 3.3 (4.22)	0.612	13.28 (4.78) vs 2.16 (4.07)	0.083	8.70 (5.30) vs 4.25 (4.59)	0.529

Continued

Table 3 Primary and Secondary Outcomes (continued)

Secondary outcomes	ITT				PP			
	Difference, baseline vs 3 mo, IVIG vs placebo	p Value	Difference, baseline vs 6 mo, IVIG vs placebo	p Value	Difference, baseline vs 3 mo, IVIG vs placebo	p Value	Difference, baseline vs 6 mo, IVIG vs placebo	p Value
Role-Emotional	1.4 (4.96) vs -3.2 (3.93)	0.471	-6.8 (5.22) vs -2.4 (5.07)	0.542	4.17 (3.40) vs -4.81 (4.24)	0.106	-4.35 (4.25) vs -3.00 (5.63)	0.849
Mental Health	2.9 (2.39) vs 1.2 (2.19)	0.596	-1.3 (3.07) vs 2.0 (2.54)	0.423	3.33 (2.57) vs 1.15 (2.36)	0.535	-1.96 (3.57) vs 2.20 (2.65)	0.355
Vitality	7.5 (3.96) vs -0.4 (1.81)	0.075	4.7 (3.47) vs 0.0 (1.90)	0.243	8.59 (3.59) vs -0.24 (1.89)	0.036	7.07 (3.78) vs 0.25 (1.99)	0.120
Bodily pain	12.0 (3.95) vs 5.9 (3.03)	0.229	7.7 (4.19) vs 2.7 (3.32)	0.358	15.31 (4.24) vs 5.73 (3.37)	0.084	11.36 (4.46) vs 3.02 (3.65)	0.156
General health	9.0 (2.95) vs 5.7 (2.59)	0.408	3.8 (2.32) vs 3.4 (2.60)	0.919	10.21 (3.41) vs 5.58 (2.81)	0.300	5.43 (2.63) vs 3.00 (2.89)	0.536
Health change	34.5 (6.73) vs 11.2 (4.90)	0.007	20.5 (5.76) vs 8.9 (4.31)	0.113	34.38 (6.87) vs 12.50 (5.42)	0.016	21.74 (6.35) vs 11.00 (4.58)	0.178
Discrete outcomes								
PGIC, n (%)		0.505		1.000		0.490		1.000
Very much improved	7 (24.1) vs 4 (14)		4 (14) vs 3 (11)		6 (25) vs 4 (15)		4 (17) vs 3 (13)	
Little or not improved	22 (75.9) vs 25 (86)		25 (86) vs 26 (89)		18 (75) vs 22 (85)		20 (83) vs 23 (87)	
RT-SFN-SIQ, n (%)		0.194		0.3574		0.340		0.355
Significant deterioration (1)	0 (0) vs 0 (0)		0 (0) vs 2 (7)		0 (0) vs 0 (0)		0 (0) vs 2 (8)	
No significant change (0)	24 (83) vs 28 (97)		26 (90) vs 25 (89)		21 (88) vs 25 (96)		21 (88) vs 22 (88)	
Significant improvement (-1)	5 (17) vs 1 (3)		3 (10) vs 1 (4)		3 (13) vs 1 (4)		3 (13) vs 1 (4)	
SFN-RODS, n (%)		0.378		0.378		0.122		0.375
Significant deterioration (-1)	2 (7) vs 4 (14)		6 (21) vs 5 (19)		0 (0) vs 3 (12)		3 (13) vs 4 (17)	
No significant change (0)	23 (79) vs 24 (83)		17 (59) vs 19 (73)		20 (83) vs 22 (85)		15 (63) vs 18 (75)	
Significant improvement (1)	4 (14) vs 1 (3)		6 (21) vs 2 (8)		4 (17) vs 1 (4)		6 (25) vs 2 (8)	
Pain-relief, n (%)		0.214		0.254		0.348		0.245
No/slight relief	19 (79) vs 17 (94)		23 (79) vs 25 (93)		16 (80) vs 16 (94)		18 (75) vs 22 (92)	
Moderate/Good/complete relief	5 (21) vs 1 (6)		6 (21) vs 2 (7)		4 (20) vs 1 (6)		6 (25) vs 2 (8)	

Abbreviations: CI = confidence interval; DSIS = daily sleep interference scale; IVIG = IV immunoglobulin; ITT = intention-to-treat; NPS = Neuropathic Pain Scale; OR = odds ratio; PGIC = patients' global impression of change; PI-NRS = Pain Intensity Numerical Rating Scale; PP = per-protocol; RT-SFN-SIQ = Rasch-transformed 13-item Small Fiber Neuropathy Symptoms Inventory Questionnaire; SF-36 = generic Short-Form 36 Health Survey; SFN-RODS = Rasch-transformed Small Fiber Neuropathy Overall Disability Scale; SFN-SIQ = Small Fiber Neuropathy Symptom Inventory Questionnaire.

Safety

Thirty patients in the IVIG group (100%) had at least 1 adverse event (table 4) compared to 29 in the placebo group (96.7%). In total, 6 serious adverse events (SAEs) were reported, including aorta coarctation repair, gastrointestinal hemorrhage, headache, hospitalization (multiple

complaints), pulmonary embolism, and suicide attempt. Only 1 SAE (aorta coarctation repair) occurred in the placebo group; the others occurred in the IVIG group. The gastrointestinal hemorrhage was diagnosed before randomization. Only 1 SAE in the IVIG group, hospitalization (multiple complaints), could have been caused by the use of

Table 4 Adverse Events

	IVIG (n = 30), n (%)	Placebo (n = 30), n (%)	p Value
Patients with at least 1 adverse event	30 (100)	29 (96.7)	1.000
All SAEs			
Aorta coarctation repair	0 (0.0)	1 (3.3)	1.000
Gastrointestinal hemorrhage	1 (3.3)	0 (0.0)	1.000
Headache	1 (3.3)	0 (0.0)	1.000
Hospitalization	1 (3.3)	0 (0.0)	1.000
Pulmonary embolism	1 (3.3)	0 (0.0)	1.000
Suicide attempt	1 (3.3)	0 (0.0)	1.000
Most common adverse events^a			
Headache	30 (100)	17 (56.7)	<0.001
Nausea	19 (63.3)	7 (23.3)	0.004
Other pain	18 (60.0)	14 (46.7)	0.438
Vomiting	11 (36.7)	0 (0.0)	0.001
Chills	9 (30.0)	3 (10.0)	0.104
Dizziness	8 (26.7)	9 (30.0)	1.000
Rash	8 (26.7)	0 (0.0)	0.005
Fatigue	7 (23.3)	11 (36.7)	0.399
Influenza	7 (23.3)	2 (6.7)	0.146
Arthralgia	4 (13.3)	6 (20.0)	0.731
Hyperhidrosis	4 (13.3)	3 (10.0)	1.000
Pyrexia	4 (13.3)	4 (13.3)	1.000
Diarrhea	3 (10.0)	0 (0.0)	0.237
Myalgia	2 (6.7)	2 (6.7)	1.000
Nasopharyngitis	1 (3.3)	2 (6.7)	1.000
Vision blurred	1 (3.3)	3 (10.0)	0.612
Cough	1 (3.3)	2 (6.7)	1.000
Migraine	0 (0.0)	2 (6.7)	0.492

Abbreviations: IVIG = IV immunoglobulin; SAE = serious adverse events.

^a Only the adverse events that occurred in at least 5% of the patients are given.

IVIG because it occurred 2 weeks after the first loading dose. The other 3 SAEs seemed not to have been caused by the use of IVIG because they occurred in the follow-up phase (2–4 weeks after the last infusion).

The adverse events that occurred in at least 5% of the patients are shown in table 4. All patients in the IVIG group (100%) had headache compared to 56.7% in the placebo group. Nausea (63.3% vs 23.3%), vomiting (36.7% vs 0.0%), and rash (26.7% vs 0.0%) occurred significantly more frequently in the IVIG group compared to the placebo group, respectively.

Because patients were allowed to use their own medications during the study (see table 1 for neuropathic pain medication use at baseline), the differences between patients with and without the use of neuropathic pain medication were investigated regarding the primary outcome (table 5). No significant differences between the groups were found.

Discussion

This is the first randomized placebo-controlled study that investigated the efficacy of IVIG in patients with painful

Table 5 Neuropathic Pain Medication During the Study

Patients using neuropathic pain medication	IVIg group, Responders vs nonresponders n (%)	p Value	Placebo group, Responders vs nonresponders n (%)	p Value
ITT population				
≥1-Point decrease in pain	8 (66.7) vs 11 (61.1)	1.000	7 (77.8) vs 11 (52.4)	0.249
≥2-Point decrease in pain	5 (71.4) vs 14 (60.9)	1.000	4 (80.0) vs 14 (56.0)	0.622
PP population				
≥1-Point decrease in pain	8 (66.7) vs 6 (50.0)	0.679	7 (77.8) vs 9 (52.9)	0.399
≥2-Point decrease in pain	5 (71.4) vs 9 (52.9)	0.653	4 (80.0) vs 12 (57.1)	0.617

Abbreviations: ITT = intention-to-treat; IVIG = IV immunoglobulin; PP = per-protocol.

I-SFN. The results of this study showed no significant effect of IVIG compared to placebo in patients with painful I-SFN. No significant differences were found in 1-point and 2-point responders on pain, PGIC, overall disability, autonomic symptoms, and pain relief. Statistically significant differences were found in maximum night pain, daily sleep interference, intense and hot pain, and some domains of the quality of life; however they were not in a consistent pattern and were not considered to be of meaningful clinical relevance in the treatment goal of this highly expensive drug. Six SAEs occurred, 5 of them in the IVIG group, and all patients in the IVIG group experienced at least 1 adverse event, of which headache, nausea, vomiting, and rash occurred significantly more frequently compared to the placebo group. All of these are adverse events of IVIG that are known to occur at rates >10%.²⁸ It can therefore be concluded that IVIG has no place in the standard treatment of painful I-SFN.

The results of this study are in contrast to open-label case series, which included many patients with an immune-mediated underlying condition,^{31-33,35-37} and a retrospective study suggesting the efficacy of IVIG in SFN.^{31,32,38} However, according to those reports, patients with SFN, without or without a clear autoimmune condition, are increasingly being treated with IVIG.³⁹ It is important to point out that certain patients with immune-confirmed SFN etiologies may benefit from IVIG treatment, and it is crucial for effective neuropathic pain treatment to perform detailed upfront testing on autoimmune diseases in patients with SFN.¹⁵ Nevertheless, future trials in these setting are necessary to determine the value of IVIG treatment in this specific cohort.

Our study has some limitations. First, the investigated cohort was relatively small and limited to patients with painful I-SFN. This outlined cohort was chosen because we aimed to demonstrate a possible proof of concept, which could be used for future studies involving larger groups of patients diagnosed with painful I-SFN. The sample size of 60 patients was calculated on the basis of the assumption that the IVIG-treated group would have a response rate of ≈60% based on the

Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials criteria⁴³ and the placebo-treated group would have a response rate of ≈25% according to a meta-analysis of the placebo effect in pain studies.⁴⁹ Second, the study was powered to find a difference between 60% response rate in the IVIG group and 25% in the placebo group. The observed score proportions were 40% and 30%, respectively, which were below our expectations and thereby underline our findings that IVIG is not a proven treatment for patients with painful I-SFN. Even though the 10% difference in response rate could be a statistically significant difference when the sample size of the study was much larger, this is not a clinically relevant difference. Third, the exclusion criteria did not describe fibromyalgia syndrome or complex regional pain syndrome, so unexpectedly, these patients could have been involved in the investigated cohort. However, before being diagnosed with SFN, some patients of our study with unexplained complaints could be (falsely) labeled as having fibromyalgia syndrome or complex regional pain syndrome because the clinical picture may show similarities, but an abnormal skin biopsy has now been found labeling them as having SFN. Fourth, our study was limited to those with painful I-SFN, so statements about IVIG to treat pain in those with autoimmune diseases underlying SFN are limited. Our results discourage the use of IVIG in this setting until randomized controlled trials are completed. Finally, although patients with psychiatric disorders were not excluded from the study, in some cases, the hospital psychiatry department was consulted before inclusion. For future IVIG treatment studies with larger groups of patients with painful I-SFN, it is recommend to assess and evaluate psychiatric comorbidity beforehand.

Some might argue that although the study was statistically negative, more (40%) in the IVIG-treated group responded than in the placebo-treated group (30%), and they would still want to treat patients to find responders. Thus, 10 patients would need to be treated with IVIG to find 1 nonplacebo responder (for the 1-point decrease in average pain) because, of the 4 of 10 who will respond to IVIG, 3 would be expected

to be a placebo responder. For the 2-point decrease in pain, 15 patients should be treated to find 1 IVIG responder. The cost per gram of IVIG in the Netherlands is €81.64.⁵⁰ For a 75-kg patient, assuming a 1-g/kg dose, the cost for this study of 5 infusions in 3 months was €30,615. Thus, finding 1 IVIG responder with a 1-point decrease in pain will cost €306,150, and finding 1 IVIG responder with a 2-point decrease in pain will cost €459,225 for 3 months only (without even taking into account the costs for the inpatient admission or home nurse visit, infusion pump, disposables, etc). Furthermore, all patients in the IVIG group experienced adverse events, including 6 SAEs, which carry significant risks and can further increase the costs associated with IVIG use.

This randomized controlled trial showed that IVIG has no significant effect on pain in patients with painful I-SFN and therefore has no role in the treatment of patients with painful I-SFN.

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Appendix (continued)

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Maurice Sopacua, MD	Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Center+, the Netherlands; Department of Rehabilitation Adelante/Maastricht University Medical Center+, the Netherlands	Screening of patients, data collection and manuscript writing
Sander M.J. van Kuijk, PhD	Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center+, the Netherlands	Data analysis, statistical analysis, and manuscript writing
Janneke G.J. Hoeijmakers, MD, PhD	Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Center+, the Netherlands	Conception, design, data collection, data analysis, and manuscript writing
Catharina G. Faber, MD, PhD	Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Center+, the Netherlands	Conception, design, data collection, data analysis, and manuscript writing
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