

IVIg for apparently autoimmune small-fiber polyneuropathy: first analysis of efficacy and safety

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Abstract

Objectives: Small-fiber polyneuropathy (SFPN) has various underlying causes, including associations with systemic autoimmune conditions. We have proposed a new cause; small-fiber-targeting autoimmune diseases akin to Guillain-Barré and chronic inflammatory demyelinating polyneuropathy (CIDP). There are no treatment studies yet for this 'apparently autoimmune SFPN' (aaSFPN), but intravenous immunoglobulin (IVIg), first-line for Guillain-Barré and CIDP, is prescribed off-label for aaSFPN despite very high cost. This project aimed to conduct the first systematic evaluation of IVIg's effectiveness for aaSFPN.

Methods: With IRB approval, we extracted all available paper and electronic medical records of qualifying patients. Inclusion required having objectively confirmed SFPN, autoimmune attribution and other potential causes excluded. IVIg needed to have been dosed at ≥ 1 g/kg/4 weeks for ≥ 3 months. We chose two primary outcomes – changes in composite autonomic function testing (AFT) reports of SFPN and in ratings of pain severity – to capture objective as well as patient-prioritized outcomes.

Results: Among all 55 eligible patients, SFPN had been confirmed by 3/3 nerve biopsies, 62% of skin biopsies, and 89% of composite AFT. Evidence of autoimmunity included 27% of patients having systemic autoimmune disorders, 20% having prior organ-specific autoimmune illnesses and 80% having $\geq 1/5$ abnormal blood-test markers associated with autoimmunity. A total of 73% had apparent small-fiber-restricted autoimmunity. IVIg treatment duration averaged 28 ± 25 months. The proportion of AFTs interpreted as indicating SFPN dropped from 89% at baseline to 55% ($p \leq 0.001$). Sweat production normalized ($p = 0.039$) and the other four domains all trended toward improvement. Among patients with pre-treatment pain $\geq 3/10$, severity averaging 6.3 ± 1.7 dropped to 5.2 ± 2.1 ($p = 0.007$). Overall, 74% of patients rated themselves 'improved' and their neurologists labeled 77% as 'IVIg responders'; 16% entered remissions that were sustained after IVIg withdrawal. All adverse events were expected; most were typical infusion reactions. The two moderate complications (3.6%) were vein thromboses not requiring discontinuation. The one severe event (1.8%), hemolytic anemia, remitted after IVIg discontinuation.

Conclusion: These results provide Class IV, real-world, proof-of-concept evidence suggesting that IVIg is safe and effective for rigorously selected SFPN patients with apparent autoimmune causality. They provide rationale for prospective trials, inform trial design and indirectly support the discovery of small-fiber-targeting autoimmune/inflammatory illnesses.

Keywords: autoimmune diseases, dysautonomia, immunotherapy, intravenous immunoglobulin, neuropathic pain, peripheral nervous system diseases

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Introduction

The polyneuropathies involve widespread damage to the body's peripheral nerves. 'Small-fiber

polyneuropathy' (SFPN), also known as small-fiber neuropathy, refers to those polyneuropathies that preferentially affect peripheral neurons with the

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thinnest axons, including the unmyelinated C-fibers, thinly myelinated A- δ somatosensory axons and the sympathetic and parasympathetic neurons. In the past, these were dichotomized as somatic *versus* autonomic, but immunohistochemical studies blurred the distinction, revealing non-sensory functions of ‘somatosensory’ axons including innervation and control of sweating, small blood vessels and bone.^{1,2} Careful evaluation showed that most patients with somatosensory complaints such as neuropathic pain, itch or sensory loss also have autonomic involvement,³ hence the current term ‘small-fiber polyneuropathy’. Applying the only population-based estimate, 52.95/100,000⁴ yields an estimated 2017 global prevalence approaching four million. This is an underestimate, since it required neurologists’ confirmation, whereas most patients remain undiagnosed. Given recent reports that SFPN underlies 40% of the fibromyalgia syndrome,^{5,6} there could there could conceivably be more than 100 million cases worldwide.

Small-fiber neurons’ multifunctionality explains why SFPN increases risk of multiple symptoms. The most common are chronic widespread pain and/or itch,⁷ postural hypotension and/or tachycardia (POTS),⁸ nausea, constipation and/or diarrhea, disordered sweating, followed by urological and sexual dysfunction. Recent studies suggest that SFPN is also associated with symptoms traditionally thought to originate in the brain, including chronic headaches and cognitive concerns.^{9,10} SFPN can even cause abnormal brain blood flow and functional connectivity that might contribute to the ‘brain fog’ some patients report.¹¹

Given these many symptoms, it can be ineffective to treat only with symptom palliation. The polypharmacy that often ensues is expensive and can cause side effects. The use of opioids to manage chronic pain has been particularly problematic. Identifying and remediating the specific medical cause in each patient is a better strategy. Small-fiber axons grow throughout life, so curtailing ongoing damage can permit them to regenerate to their varied targets. One treatment can improve and sometimes improve or resolve multiple symptoms and dysfunctions.

Because small-fiber axons are long and thin, they are vulnerable to disruptions in axon maintenance by any medical problem, and SFPN has more than a dozen medical causes.¹² Diabetes, the most common cause in developed countries, is estimated to

cause half of small-fiber predominant neuropathy.¹³ The second largest group of SFPN patients, estimated at 20–50%,^{4,14–17} comprises patients with no apparent cause at first evaluation; so-called ‘cryptogenic’ or ‘initially idiopathic’ SFPN (iiSFPN). Ameliorating or curing diabetes mitigates complications including neuropathy,¹⁸ as do disease-modifying treatments for nutritional, toxic and infectious causes, but there are no options for the 30–50% of patients with iiSFPN.

We and others have suggested that autoimmunity and inflammation play a far greater role in iiSFPN than recognized. Systemic autoimmune conditions linked to SFPN include lupus, rheumatoid arthritis, sarcoidosis, vasculitis and celiac.^{19–35} Sjögren’s is the most common among these. Virtually nothing is known about how systemic autoimmune diseases affect small fibers.^{36–38}

We have proposed a new cause of iiSFPN – autoimmunity specifically targeting small-fiber epitopes. Given the current lack of proof, we call this ‘apparently autoimmune’ SFPN (aaSFPN). This concept is biologically plausible, akin to the well-characterized acute and chronic large-fiber-targeting autoimmune diseases Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor mononeuropathy (MMN).^{39,40} The current very limited evidence about mechanisms suggests that autoantibodies and complement consumption^{3,12} are more important than cytotoxic T-cell attack. This discovery has important implications for medical care, given the prevalence and disability of SFPN, and the widespread availability and proven efficacy of old and new immunotherapies for autoimmune neuropathies.

The concept of aaSFPN began with reports of a few iiSFPN patients who responded to treatment with corticosteroids or pooled human intravenous immunoglobulins (IVIg).^{41–44} The first case series found corticosteroids efficacious in 10/15 SFPN patients (67%), with improvement in symptoms plus objective tests.³ Since prolonged corticosteroids can cause complications, IVIg is increasingly prescribed off-label for aaSFPN. It is a first-line treatment for GBS, CIDP, and MMN^{45–48} that modifies B- and T-cells, inhibits antibody production and interferes with the complement cascade. Most nerve specialists know how to manage IVIg, and dosing parameters were established in trials such as the Immune Globulin Intravenous

CIDP Efficacy (ICE) trial, a large double-blind, placebo-controlled, randomized crossover trial.⁴⁹ In addition to confirming efficacy, these trials established the safety outcomes and dosing algorithms we applied here.^{50,51}

All of the earlier small series document favorable outcomes from IVIg treatment of SFPN, for instance in three patients with associated celiac,⁵² three with sarcoidosis,⁵³ and six with Sjögren's syndrome.^{54,55} In our case series of early-onset SFPN, 5/8 (62%) improved clinically with early evidence of improved skin biopsies and AFT.³ A multicenter, double-blind trial of IVIg in 23 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) reported efficacy for pain, a secondary outcome.⁵⁶

However, supplies of IVIg are limited, administration is difficult and yearly cost can exceed \$100,000, so insurers do not usually pay for treatment of SFPN. Plus, IVIg often causes infusion reactions and rarely causes serious adverse events.⁵⁷ Systematic studies are needed, and the first randomized, double-blind, placebo-controlled, clinical trial of IVIg for idiopathic small-fiber neuropathy has begun recruitment in Europe.⁵⁸ However, interim data are urgently needed now to guide clinical practice and reimbursement decisions.

To gain insights from currently available data, we performed structured abstraction from medical records to generate the first large case series for analysis. We chose change in pain severity as a primary outcome because chronic pain is arguably the most disabling symptom of SFPN and one of great concern to patients. Plus, validated patient-reported pain scores were routinely collected.⁵⁹ However, pain is a subjective patient-reported outcome that is highly susceptible to placebo effects, so we judged it prudent to include an objective outcome that could not be influenced by patient expectations. The strongest candidates were PGP9.5-immunolabeled skin biopsies from the lower leg and composite autonomic function testing (AFT), which have been endorsed for diagnosing SFPN by major neurological societies.^{60,61} We selected AFT given the high prevalence of potentially dysautonomic symptoms in SFPN, recommendations to measure autonomic as well as somatic dysfunction when assessing small-fiber neuropathies⁶² and prior use of AFT in assessing systemic autoimmune SFPN.³¹ For secondary outcomes, we extracted all safety data,

demographic data, relevant blood-test results, plus patients' and physicians' impressions of change, all generally reported in treatment trials. So far as we know, this is the first systematic study of IVIg treatment for 'idiopathic' SFPN.

Methods

Standard protocol approvals, registrations and patient consents

All protocols were approved by the hospital's IRB, which waived informed consent.

Study design, case definitions and baseline patient characteristics

Since there are no consensus case definitions, to identify potential subjects we screened the records of every patient evaluated for SFPN in our hospital-based peripheral-nerve practice since our index case⁴² through 31 December 2015 and developed rigorous research-oriented preliminary case definitions for SFPN, for iiSFPN and for aaSFPN.

Inclusion required meeting our case definition of 'definite SFPN', which required physician's clinical diagnosis plus objective confirmation of diagnosis by distal-leg PGP9.5-immunolabeled skin biopsy, surgical nerve biopsy or AFT. Since these studies had been performed in diverse facilities, to add rigor we accepted only original reports and interpretations from JC-accredited clinical labs using standard approved methods and analyses. Skin biopsy diagnosis required density of epidermal nerve fibers below the fifth centile of predicted.^{60,61} For nerve biopsies, diagnosis requires qualitative or morphometric evidence of reduced unmyelinated and/or thinly myelinated axons, prior axonal degeneration in the form of empty Schwann cell stacks, collagen pockets, and sometimes excess inflammatory cells and clusters of regenerating axons.^{43,60,63,64} Diagnosis by composite AFT requires appropriate abnormalities in $\geq 2/4$ domains: heart rate variability during deep breathing (HRDB); heart and blood-pressure responses to Valsalva maneuver and to vertical tilt; and quantitative sudomotor axon reflex testing (QSART).^{60,65}

For inclusion, patients also had to meet the case definition of apparently autoimmune SFPN (aaSFPN) we developed. In addition to definite SFPN, this required systematic exclusion of non-immune

causes by medical history, exam and results of recommended blood tests.¹² We routinely evaluated for diabetes, prediabetes, thyroid disorders, abnormal vitamin levels, Sjögren's, celiac, hepatitis, Lyme disease and monoclonal gammopathies, plus less-common potential causes suggested by individual histories or examinations. Then it required objective evidence of dysimmunity.

We currently recognize two types of aaSFPN: that associated with systemic autoimmunity (either a recognized systemic inflammatory condition, or evidence of more than one organ-specific condition); and autoimmunity apparently restricted to small fibers. For patients to be classified with systemic rheumatologic disorders, we preferred a rheumatologist's consultation. For diagnoses of organ-specific autoimmune disorder (e.g. Hashimoto's thyroiditis), we preferred diagnoses made by a primary care provider or appropriate subspecialist using accepted clinical criteria. Our case definition of 'systemic aaSFPN' thus required having no other apparent cause of neuropathy, plus either a systemic rheumatologic disorder, or autoimmune disease affecting at least one other organ system.

Classification of a patient as having nerve-specific aaSFPN was more speculative, and rheumatologists were often consulted. This case definition also required no other apparent cause of neuropathy, no systemic rheumatologic diagnosis, plus objective supporting evidence including inflammatory infiltrates within nerve or skin biopsies. Persistent, otherwise unexplained blood-test markers of dysimmunity/inflammation were also accepted. These comprised anti-nuclear antibodies (ANAs, conservatively defined as $\geq 1:160$ dilution), elevated erythrocyte sedimentation rate (ESR; ≥ 15 mm/h), low complement component 4 (C4; < 20 mg/dl), low complement component 3 (C3; < 85 mg/dl) and Sjögren's autoantibodies (SSA/Ro, SSA/La). In addition to pathology and serology, we also accepted clear improvement in neuropathy from prior immunotherapy, as in our index case.⁴²

The additional requirement for study inclusion was an adequate trial of IVIg, specifically treatment initiated at doses ≥ 1 g/kg/4 weeks, the standard for autoimmune neuropathies.⁴⁵ For efficacy analyses, patients had to have been treated for at least 3 months. The safety analysis included every patient regardless of treatment duration.

Data collection

The variables extracted and analyzed were demographics, medical histories, results of blood tests for neuropathy causes, pain severity ratings, interpretations of composite AFT and individual domain parameters, details of IVIg dosing, adverse events (AEs), patients' global impression of change (PGIC), physicians' assessment of benefit and detailed analyses of all safety events and treatment discontinuations.

The first primary outcome was pain severity, rated at each visit with the standard 11-point numeric scale, with 0 representing 'no pain' and 10 'worst pain'.⁵⁹ The primary analysis included all patients with baseline pain $\geq 3/10$. The post-treatment pain scores reported are the mean of all available pain scores gathered during treatment. The other co-primary outcome was the reported clinical interpretation of AFT results as diagnostic of SFPN.

The secondary outcomes were: (1) safety – all AEs or infusion reactions were abstracted and rated as mild, moderate or severe according to guidelines;⁶⁶ (2) standard demographic characteristics; (3) pertinent medical histories and results of diagnostic testing; and (4) the standard seven-point PGIC.⁶⁷ The clinic routinely collected the PGIC, using these instructions: 'Based on your own impression, please check the best description of the overall change in your illness in the last month. Score this regardless of what you think caused the change.' Response items ranged from 1 ('my illness is very much better') to 7 ('my illness is very much worse'), with 4 representing 'there has been no change in my illness'. Secondary outcome 5 was physicians' impression of whether patients were IVIg 'responders' or 'non-responders' as extracted from their notes. Outcome 6 – treatment duration – reflected not only the balance of positive and negative effects, but often the availability of insurance reimbursement. Outcome 7 comprised reasons for any treatment discontinuation.

Statistical analyses

The SPSS for Windows version 19 package (SPSS Inc., Chicago, IL, USA) was used. The Shapiro–Wilk test established that pain ratings were normally distributed so parametric two-tailed *t* tests were used. Means \pm standard deviations described central tendencies. McNemar tests were used for paired nominal data such as

within-subject repeat AFT interpretations. Chi-square tests compared categorical variables. Tests were considered significant at $p \leq 0.05$, although a Bonferroni correction was applied for determining evidence of treatment efficacy. Because there were two primary outcomes, $p \leq 0.025$ was required for statistical significance.

Results

Cohort characteristics

A total of 78% of the subjects (43/55) identified as female. Their age at baseline averaged 41 ± 17 years (range 6–85 years). At baseline, reports from 89% (39/44) of their AFTs, 61% (31/49) of their distal-leg skin biopsies and 3/3 sural nerve biopsies supported a diagnosis of SFPN. Among the four AFT domains, QSART sweat production, considered most specific for SFPN, was the one most often abnormal, in 69% of patients. Among the 17 patients with skin biopsies interpreted as normal and baseline AFT results available, 88% had abnormally reduced sweating. A total of 60% (33/55) had had their SFPN confirmed by one test; it had been confirmed by two tests in 38% (21/55); and 2% (1/55) had confirmation from all three tests. The latency between onset of SFPN symptoms to start of IVIg treatment averaged 6.3 ± 6.3 years (range 0.3–33 years). A total of 35% of patients had received Gammagard, 38% had received Gamunex, 6% had received Privigen and 4% had received Gammaked. Doses during the first 3 months of treatment ranged between 1.3–2.0 g/kg/4 weeks, after which doses were usually slowly titrated downwards in patients who continued treatment.

Regarding the attribution of SFPN to autoimmune causes, 27% (15/55) of these patients had systemic autoimmune diagnoses. Eight had been diagnosed with Sjögren's syndrome, four with systemic lupus erythematosus, two with rheumatoid arthritis and one with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). A total of 20% (11/55) had other organ-specific autoimmune conditions, specifically five with Hashimoto's thyroiditis, three with inflammatory bowel diseases and one each with type 1 diabetes, Grave's disease and psoriasis. Regarding serologic markers suggestive of autoimmunity, 80% (45/56) of patients had one or more abnormal blood-test result consistent with dysimmunity. Specifically, 35% had ANAs ($\geq 1:160$ dilution), 33% had elevated ESR (≥ 15

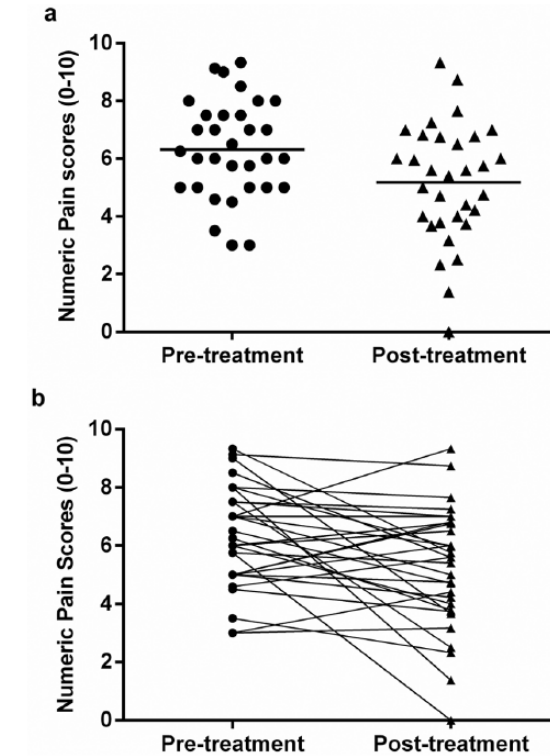


Figure 1. Pain scores before and during IVIg treatment. (a) Circles represent pain scores before treatment, triangles represent pain scores during IVIg treatment and lines represent group averages. (b) Each individual patient's change in pain scores.

mm/h), 28% had low C4 (<20 mg/dl), 14% had low C3 (<85 mg/dl) and 11% had Sjögren's autoantibodies (SSA/Ro, SSA/La). Additionally, 28% had IgG deficiency (IgG <614 mg/dl), 18% had IgG subclass deficiency, 14% had IgM deficiency (IgM <53 mg/dl) and 11% had IgA deficiency (IgA <69 mg/dl).

Primary (efficacy) outcomes

Four subjects discontinued IVIg within the first 3 months of treatment because of infusion reactions, so the efficacy sample comprised 51 patients. As shown in Figure 1, among the 32 with baseline pain $\geq 3/10$, baseline pain severity averaging 6.3 ± 1.7 dropped to 5.2 ± 2.1 during treatment ($t = 2.875$; $p = 0.007$). A total of 31% (10/32) had $\geq 30\%$ reduction in pain, with their scores dropping on average 3.9 ± 1.9 points. As shown in Figure 2, among all 35 patients with pre- and post-treatment AFT results available, the proportion with AFT results that had been interpreted as indicating SFPN dropped from 89% (31/35) at baseline to 57% (20/35;

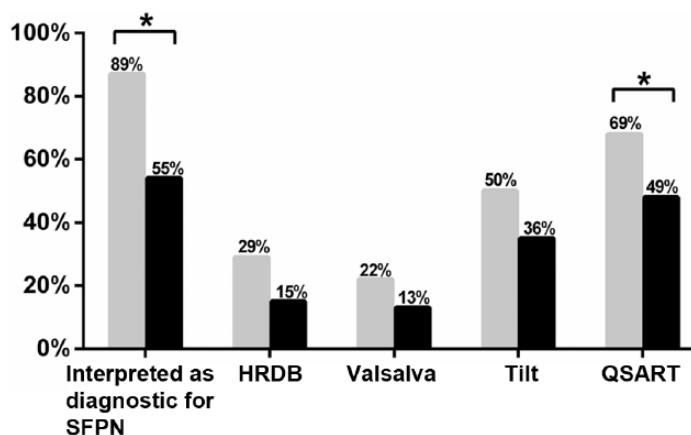


Figure 2. Prevalence of abnormal results of composite autonomic function testing (AFT). Gray bars represent the percentage of patients with abnormal results at baseline before IVIg treatment. Black bars represent the percentage of patients with abnormal results during treatment. * represents $p < 0.05$.

$p = 0.026$) during treatment, a 31% response rate. Among the four autonomic domains tested, QSART improved significantly ($p = 0.039$). The other AFT subtests showed non-significant trends toward improvement. Thus, both of the study's two primary outcomes provided congruent evidence of efficacy.

Secondary outcomes

Safety. A total of 75% (41/55) of patients reported a treatment-incident AE. Among these, 65% (36/55) were typical transient infusion reactions. Specifically 60% reported headache, 35% reported nausea, 35% reported influenza-like symptoms and 20% reported stiff neck. These led three patients to stop IVIg before completing the intended 3-month trial. Of note, one later retried IVIg, tolerated it well and reported benefit, but the outcome of this second trial was not included in the analysis. Most infusion reactions were effectively managed using standard strategies – for example, slowing infusion rates, augmenting hydration and administering standard co-medications. There were two moderate AEs (3.6%), which were both vein thromboses (DVT), a known complication of IVIg.⁶⁸ Neither caused embolic complications. One clot developed in a subclavian vein containing an indwelling catheter placed for access. That patient continued IVIg after co-administration of warfarin followed by aspirin. The other developed in an arm vein used for peripheral administration of IVIg. It did not require discontinuing IVIg or any specific treatment. There was one serious AE (1.8%), which was new hemolytic

anemia that resolved after transfusion and discontinuing IVIg. Hemolytic anemia is a known complication of IVIg.^{57,69–71}

Patients' and physicians' impressions of change

Analysis of standard seven-point PGIC scores indicated that 3% (1/31) of patients rated themselves as 'very much improved', 39% (12/31) as 'much improved', 32% (10/31) as 'mildly improved', 16% (5/31) as 'unchanged', 3% (1/31) as 'slightly worse', and 7% (2/31) as 'much worse'. None rated themselves as 'very much worse'. Overall, 74% (23/31) rated themselves as improved and 10% (3/31) as worse. Physicians labeled 77% (39/51) of patients as 'IVIg responders' and 23% (12/51) as 'non-responders'. Males were more often responders than females (100% versus 63%; $p = 0.009$). A total of 16% of patients (8/51) experienced such profound improvement that they were able to wean and then discontinue IVIg while maintaining benefit. They had been in remission for 20 months on average as of 31 December 2015.

Treatment duration and discontinuations

Through 31 December 2015, the average duration of IVIg treatment was 27 ± 25 months (range 1–114 months; Figure 3). The 39 'responders' were treated on average for 38 ± 23 months (range 3–114 months). Twenty-nine had continued IVIg with gradual improvement and eight had stopped IVIg after remission. In two others, insurers withdrew approval for reimbursement despite documented improvement and patients'

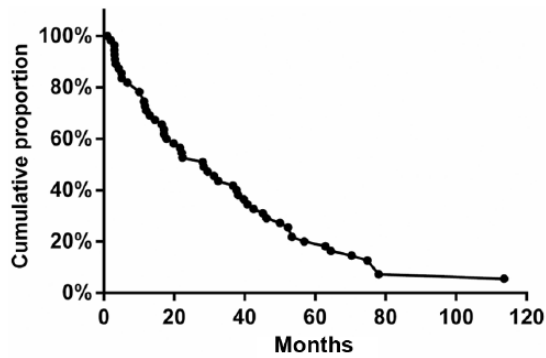


Figure 3. Duration of IVIg treatment.

desire to continue treatment. Among the 13 non-responders, eight had discontinued IVIg by 31 December 2015 because of ineffectiveness or insufficient effectiveness to justify continuing, and three because of infusion reactions.

Discussion

This first systematic study of IVIg treatment of SFPN met the overall (combined) study criteria for efficacy, plus both of the two complementary primary efficacy outcomes. All seven secondary outcomes provided additional evidence of efficacy and safety. Patients and physicians each rated 3/4 of patients as improved, and 16% of patients entered sustained remission that permitted IVIg withdrawal. The profile of AEs was similar to prior reports.⁷² Together, these results provide proof-of-concept and preliminary rationale for medical use of high-dose IVIg therapy in rigorously selected patients with confirmed SFPN attributed to autoimmunity (aaSFPN). They also imply that aaSFPN may be far more common than appreciated, and they provide strong evidence that medical insurers should no longer reflexively decline to pay for IVIg treatment of aaSFPN.

This study generated insights. First, three-quarters of the included patients were classified with ‘restricted’ small-fiber autoimmunity, with only one-quarter having systemic autoimmune diagnoses. Of note, one-third of all Sjögren’s cases have an initial neurologic presentation.⁷³ Some of our participants later received systemic diagnoses, but most did not during the study. This supports our hypothesis of small-fiber-targeting autoimmunity, and suggests it may be a common cause of iiSFPN. Plus it demonstrates the need to formalize case definitions for SFPN and aaSFPN.

These are prerequisites for clinical trials and basic research into mechanisms and identification of small-fiber epitopes. This study also generated the first remission rate for aaSFPN; 16% after IVIg treatment. We are not aware of prior remission rates for any type of SFPN, much less for aaSFPN, so remissions cannot be definitively ascribed to IVIg without comparator data from observational natural history studies that include untreated patients.

The blood-test analyses also were informative. The fact that 80% of patients had at least one abnormal result consistent with dysimmunity supports clinical use of these tests. Since these abnormalities helped support the decision to administer IVIg, and thus inclusion in the study cohort, there is circular reasoning. However, we earlier reported similar prevalences (28% with high ANA, 28% with high ESR, 16% with low C4, 11% with low C3 and 9% with Sjögren’s serologies) among an unselected group of 195 patients with confirmed iiSFPN from all causes.¹² Also, as far as we know, these results are the first association of aaSFPN with immunoglobulin deficiency. It was unexpected to find 28% with IgG deficiency, 18% with IgG subclass deficiencies, 14% with IgM deficiency and 11% with IgA deficiency. It is unknown whether these were primary or secondary, whether genetic or autoimmune, but if confirmed, this additionally links B-cell dysfunction with aaSFPN.

One strength is this study’s exploratory use of two complimentary primary outcomes, both of which improved significantly. This allowed one study to encompass both the somatic and autonomic aspects of SFPN and to balance patient-reported and objective/functional measures. Including an objective outcome meant that benefits could not be ascribed only to placebo. Given the lack of one universal symptom of SFPN, this study supports use of multiple efficacy outcomes. Although not all participants had chronic pain, this seems essential to capture given its prevalence, associated disability, and the relative inefficacy and serious adverse effects of long-term use of pain-relievers. Another strength is that all subjects had objective confirmation of diagnosis. We consider this necessary for long-term immunomodulation, given the non-specificity of SFPN symptoms and the expense and potential adverse effects of immunotherapies. However, we seek less expensive and more practical objective biomarkers.

This study's major limitation is that it is a retrospective study that provides only Class IV evidence.⁷⁴ An inherent limitation in 'real-world' studies is variation in dosing and assessment parameters. Here, the initial target dose was 2.0 g/kg/4 weeks, as in all five major placebo-controlled trials of IVIg for CIDP.^{49,75–78} We and others find it more efficient to trial the highest recommended dose, and then titrate downwards, rather than to try low doses that, if ineffective, often engender retrials of higher doses.⁵¹ Other potential contributors to dosing variability included potentially inaccurate patient weights, rounding doses and dose individualizations for reasons including tolerability. The actual initial doses, all 1.3–2.0 g/kg/4 weeks, were within the range used in clinical trials for CIDP,⁴⁵ and similar to the mean 1.4 ± 0.6 g/kg/4.3 weeks dose optimal for CIDP and MMN.⁵¹ Another study strength is that patients were treated for at least 3 months before assessing efficacy, as single-dose trials are now considered insufficient. Lastly, to facilitate data aggregation patients were reassessed at standard intervals; 3 months for initial prescriptions or after dose changes, and 6 months after same-dose refills.

Although IVIg was initially prescribed in 4-week cycles (from day 1 of each infusion), actual infusion days sometimes varied. Cycle length was sometimes shortened to resolve end-of-cycle wearing off and during tapering, sometimes cycle lengths were increased to 5–6 weeks. These intervals correspond well to the 4.3 week mean cycle length reported in optimized CIDP and MMN patients.⁵¹ We always reported doses in g/kg/4 weeks to control for cycle length. The parameters used here may inform medical use as well as trial design.

How do the efficacy and safety results compare to those reported in other immune polyneuropathies? The large IVIg trials for large-fiber demyelinating polyneuropathy had similar response rates; 53% in CIDP,⁷⁹ 53% in GBS⁸⁰ and 78% in MMN.⁴⁸ The current study's safety profile also compares well to published data.⁸¹ The 60% prevalence of infusion reactions here corresponds favorably to 75–77% prevalence elsewhere.^{49,82} The one serious AE, hemolytic anemia, is established, with incidence ~1 per 1000 IVIG treatment episodes,⁵⁷ and the 1.8% prevalence of DVT here compares well to the 11.3% rate in the one large study of thromboembolic complications of IVIg for neuropathy.⁶⁸

This study helped us develop interim case definitions and treatment guidelines that may be useful clinically. *Definite SFPN* requires a physician's impression based on history and exam plus objective confirmation from a consensus-recommended objective test. *Apparently autoimmune SFPN* requires systematic exclusion of non-immune causes including with blood tests,¹² plus evidence of autoimmune association. *Systemic aaSFPN* requires diagnosis (prior or concurrent) of a neuropathy-associated rheumatologic disorder. In patients without systemic autoimmunity, diagnosing *small-fiber restricted aaSFPN* requires blood-test or pathological evidence of dysimmunity/inflammation, or prior response to immunotherapy.

Additional considerations in selecting candidates for IVIg include (1) physician impression that the aaSFPN is disabling and not improving; (2) no substantial improvement from no treatment or conventional treatment of symptoms; (3) no contraindications to IVIg; and (4) patient preference. Until trial results are published, this study provides rationale for appropriate medical prescribing and insurer coverage of repeated high-dose immunoglobulin treatment for carefully selected patients with apparently autoimmune small-fiber polyneuropathy.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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