Long-term Effectiveness of IVIg Maintenance Therapy in 36 Patients With GAD Antibody–Positive Stiff-Person Syndrome

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Abstract

Background and Objectives
IVIg has been the preferred immunotherapy in stiff-person syndrome (SPS) based on a 3-month controlled trial, but whether it is also effective in inducing long-term benefits or arresting disease progression is unknown. The information is needed because SPS is a progressively disabling disease and IVIg is liberally used as chronic therapy without efficacy data. The present study explores the long-term effects of IVIg in the largest cohort of well-characterized patients with SPS followed by the same clinicians over 10 years.

Methods
Data of 36 patients (32 glutamic acid decarboxylase [GAD] positive), diagnosed and treated with monthly maintenance IVIg by the same neurologists, were analyzed. Response was assessed by physician-observed changes, patients’ reports of symptom improvement, modified Rankin Scale (mRS) scores, and dependency trials evaluating symptom recurrence after stopping IVIg, prolonging infusion frequency, decreasing monthly dose, or wearing-off effects in between doses. Clinically meaningful long-term response was defined by improved mRS scores, improvement in physician-assessed stiffness, balance and gait, and functional decline with dependency trials.

Results
Twenty-four of 36 (67%) patients had clinically meaningful response over a median 40-month period. Patients with improved mRS scores by 1–2 points manifested improved gait, posture, balance and decreased stiffness, spasms, and startle response; some patients using a wheelchair and those ambulating with devices walked unassisted. In 25% of responders, treatment benefit was sustained for a 40-month median period, but in 29.1%, it declined over a 39-month period; 12.5% exhibited a conditioning effect. Three of 5 patients with cerebellar GAD-SPS variant also improved over time. The 12 patients who did not respond the first 3 months remained unresponsive even if IVIg continued for several months.

Discussion
This is a large study in 36 patients with SPS demonstrating that monthly maintenance IVIg therapy offers long-term benefits in 67% of patients for a median 3.3-year period. Because 29.1% experienced diminishing benefit over time due to disease progression, the study highlights the need for more effective therapies.
Stiff-person syndrome (SPS) is an autoimmune disorder characterized by simultaneous contraction of agonist and antagonist muscles, resulting in muscle rigidity and stiffness. Diagnostic criteria for SPS include stiffness of the limbs and axial muscles, particularly abdominal and thoracolumbar paraspinal; superimposed painful spasms precipitated by emotional distress or unexpected tactile or auditory stimuli; and high (>1: 10,000 by ELISA) serum antiguiltamic acid decarboxylase (GAD)-65 antibody titers in up to 80% of the patients. Detailed follow-up data from 53 sequentially studied patients have shown that without immunotherapy, SPS is a progressive disease leading to cumulative physical disability over time even with the use of antispasmodic medications such as baclofen, diazepam, and gabapentin.

Among the immunotherapeutic agents, high-dose intravenous immunoglobulin (IVIg) is currently the preferred treatment for patients with SPS who do not achieve symptom control with muscle relaxants and benzodiazepines, based on a placebo-controlled randomized trial that had shown that high-dose IVIg significantly improves stiffness, spasms, and gait, over a 3-month study period. Because SPS is a progressive disease, IVIg is currently used as a chronic monthly treatment, although long-term efficacy data are lacking. As a result, there is significant overuse while a placebo or conditioning effect, common in one-third of patients receiving chronic IVIg therapy, is likely overlooked.

Considering that SPS is a rare disease, it is not practical to perform a prospective long-term controlled study, while giving placebo over long periods may raise clinical ethics issues. Careful data collection in well-characterized patients followed by the same physicians using dependency tests to distinguish true treatment benefit from a conditioning or a placebo effect, as previously witnessed in a controlled study with rituximab, is a realistic option to document long-term efficacy. Apart from 2 small studies with 2–5 patients over short time periods using subcutaneous immunoglobulin, there is only one relatively large size study in 19 patients receiving IVIg that was based on retrospective data collected using a patient-reported scoring system without performing dependency tests to objectively assess efficacy.

The present study describes long-term data from the largest cohort of patients with SPS treated monthly with IVIg and followed over the last 10 years at a single academic center by the same clinicians with expertise in SPS, including the performance of 2 controlled trials, adhering to the same clinical criteria. Importantly, this is also the first study evaluating long-term IVIg benefits trying to distinguish treatment response from placebo or conditioning effects by performing IVIg dependency trials.

Methods
All adults over the age of 18 with typical SPS, diagnosed by the same neurologists based on the previously published diagnostic criteria and followed in our clinic within the last 10 years (2011–2021) were included in the study analysis. All patients received IVIg as prescribed and monitored by the same lead clinician and/or his trainees.

Data collected included demographic information, anti-GAD Ab status, when symptoms started, duration and doses of treatment with IVIg, patients’ subjective treatment response, physician-observed effects of IVIg, frequency of dependency trials (or their equivalent), modified Rankin Scale (mRS) scores, and estimated duration of meaningful benefit from IVIg. Response to IVIg was analyzed using both patients’ subjective report of symptom improvement and physician assessments. After initiation of IVIg, patients underwent dependency trials when clinical improvement plateaued to confirm continuing need for therapy. A formal dependency trial was performed in patients receiving IVIg by holding doses, prolonging the frequency of IVIg infusions to more than 4 weeks, or decreasing the monthly IVIg dose to assess for recurrence of symptoms or regression of symptom severity, as previously discussed. Other equivalents to a formal dependency trial involved missed doses due to insurance issues or the COVID-19 pandemic or observing a wearing-off effect in between IVIg doses. Of importance, the subgroup analysis was precisely performed to distinguish the patients who did not undergo dependency trials from those who did. A modified Rankin Scale score was calculated based on documentation before starting IVIg, after the first few months of full IVIg dose, and at follow up visits while on maintenance therapy to evaluate for functional improvement. A clinically meaningful response to IVIg was defined by a change in the mRS score after IVIg treatment; improvement in physician-assessed stiffness, balance, and gait; or a decline in stiffness, balance, gait, and daily functioning with dependency trials. Duration of meaningful benefit was calculated based on patient and physician assessment of when treatment with IVIg no longer produced clinically meaningful changes.

IVIg dosing was also taken into consideration based on the information available in the records. Every patient was generally treated first with an IVIg dose of 2 g/kg of body weight...
### Table 1 Characteristics of Patients With SPS Who Responded to Long-term IVIg Maintenance Therapy (IVIg Responders)

<table>
<thead>
<tr>
<th>ID #</th>
<th>Age/sex</th>
<th>Time from symptom onset to diagnosis (y)</th>
<th>Time from symptom onset to treatment with IVIg (y)</th>
<th>GAD antibody positivity</th>
<th>Type of responder</th>
<th>Dependency trials</th>
<th>Total duration of IVIg (mo)</th>
<th>Estimated duration of clinical benefit (mo)</th>
<th>IVIg benefit</th>
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<tbody>
<tr>
<td>R1</td>
<td>55/F</td>
<td>9</td>
<td>11</td>
<td>GAD Ab (+)</td>
<td>Continued benefit</td>
<td>Wearing-off effect</td>
<td>38</td>
<td>38</td>
<td>Decreased spasms and improved gait</td>
</tr>
<tr>
<td>R2</td>
<td>41/F</td>
<td>0</td>
<td>0</td>
<td>GAD Ab (+)</td>
<td>Continued benefit</td>
<td>Wearing-off effect</td>
<td>42</td>
<td>42</td>
<td>Decreased spasms and improved gait (mRS score 4 → 2)</td>
</tr>
<tr>
<td>R3</td>
<td>32/F</td>
<td>14</td>
<td>Cannot determine</td>
<td>GAD Ab (+)</td>
<td>Continued benefit</td>
<td>Wearing-off effect</td>
<td>At least 55</td>
<td>At least 55</td>
<td>Decreased spasms</td>
</tr>
<tr>
<td>R4</td>
<td>49/F</td>
<td>1</td>
<td>1</td>
<td>GAD Ab (+)</td>
<td>Continued benefit</td>
<td>None, recently started IVIg</td>
<td>13</td>
<td>13</td>
<td>Decreased stiffness and back pain; improved gait (mRS score 3 → 2)</td>
</tr>
<tr>
<td>R5</td>
<td>54/F</td>
<td>2</td>
<td>4</td>
<td>GAD Ab (+)</td>
<td>Continued benefit</td>
<td>None</td>
<td>At least 28</td>
<td>At least 28</td>
<td>Improved function and gait (mRS score 4 → 3)</td>
</tr>
<tr>
<td>R6</td>
<td>78/F</td>
<td>11</td>
<td>14</td>
<td>GAD Ab (+)</td>
<td>Continued benefit</td>
<td>Wearing-off effect</td>
<td>62</td>
<td>62</td>
<td>Unspecified</td>
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<tr>
<td>R7</td>
<td>47/F</td>
<td>3</td>
<td>3</td>
<td>GAD Ab (+)</td>
<td>Decreasing benefit</td>
<td>Wearing-off effect; decreased frequency</td>
<td>41</td>
<td>19</td>
<td>Improved walking, stiffness, flexibility, facial expression, and dysarthria</td>
</tr>
<tr>
<td>R8</td>
<td>59/F</td>
<td>Cannot determine</td>
<td>Cannot determine</td>
<td>GAD Ab (+)</td>
<td>Decreasing benefit</td>
<td>Wearing-off effect</td>
<td>At least 16</td>
<td>Cannot determine</td>
<td>Unspecified</td>
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<tr>
<td>R9</td>
<td>40/F</td>
<td>7</td>
<td>8</td>
<td>GAD Ab (-)</td>
<td>Decreasing benefit</td>
<td>Wearing-off; decreased frequency and dose</td>
<td>22</td>
<td>22</td>
<td>Increased energy; decreased pain and spasms; improved gait</td>
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<tr>
<td>R10</td>
<td>72/F</td>
<td>26</td>
<td>26</td>
<td>GAD Ab (+)</td>
<td>Decreasing benefit</td>
<td>Missed dose due to COVID</td>
<td>63</td>
<td>50</td>
<td>Improved gait and balance; decreased spasms; decreased pain (mRS score 3 → 2)</td>
</tr>
<tr>
<td>R11</td>
<td>53/M</td>
<td>1</td>
<td>1</td>
<td>GAD Ab (+)</td>
<td>Decreasing benefit</td>
<td>6-mo gap without insurance</td>
<td>31</td>
<td>31</td>
<td>Improved gait and walking speed and faster speech (mRS score 4 → 3)</td>
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<tr>
<td>R12</td>
<td>57/F</td>
<td>1</td>
<td>1</td>
<td>GAD Ab (+)</td>
<td>Decreasing benefit</td>
<td>Decreased frequency during COVID</td>
<td>121</td>
<td>Cannot determine</td>
<td>Improved pain, stiffness, and gait</td>
</tr>
<tr>
<td>R13</td>
<td>59/M</td>
<td>1</td>
<td>2</td>
<td>GAD Ab (+)</td>
<td>Decreasing benefit</td>
<td>Wearing-off effect; dose held</td>
<td>39</td>
<td>39</td>
<td>Improved balance and gait; decreased rotary nystagmus and rigidity</td>
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<tr>
<td>R14</td>
<td>60/F</td>
<td>6</td>
<td>8</td>
<td>GAD Ab (+)</td>
<td>No dependency trial</td>
<td>None</td>
<td>At least 58</td>
<td>Cannot determine</td>
<td>Decreased stiffness and spasms</td>
</tr>
<tr>
<td>R15</td>
<td>73 (now deceased)/F</td>
<td>4</td>
<td>0</td>
<td>GAD Ab (+)</td>
<td>No dependency trial</td>
<td>None</td>
<td>143</td>
<td>Cannot determine</td>
<td>Unspecified</td>
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<tr>
<td>R16</td>
<td>56/F</td>
<td>2</td>
<td>4</td>
<td>GAD Ab (+)</td>
<td>No dependency trial</td>
<td>None</td>
<td>90</td>
<td>Cannot determine</td>
<td>Improved gait; decreased stiffness and spasms (mRS score 4 → 2)</td>
</tr>
<tr>
<td>R17</td>
<td>51/F</td>
<td>7</td>
<td>8</td>
<td>GAD Ab (+)</td>
<td>No dependency trial</td>
<td>None</td>
<td>At least 23</td>
<td>Cannot determine</td>
<td>Improved gait, decreased stiffness</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>ID #</th>
<th>Age/sex</th>
<th>Time from symptom onset to diagnosis (y)</th>
<th>Time from symptom onset to treatment with IVIg (y)</th>
<th>GAD antibody positivity</th>
<th>Type of responder</th>
<th>Dependency trials</th>
<th>Total duration of IVIg (mo)</th>
<th>Estimated duration of clinical benefit (mo)</th>
<th>IVIg benefit</th>
</tr>
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<tbody>
<tr>
<td>R18</td>
<td>57/F</td>
<td>0</td>
<td>0</td>
<td>GAD Ab (+)</td>
<td>No dependency trial</td>
<td>None</td>
<td>13</td>
<td>Cannot determine</td>
<td>Decreased stiffness</td>
</tr>
<tr>
<td>R19</td>
<td>74/F</td>
<td>1</td>
<td>1</td>
<td>GAD Ab (+)</td>
<td>Conditioning effect</td>
<td>Dose held; dose decreased</td>
<td>58</td>
<td>54</td>
<td>Improved gait and mobility; decreased stiffness and pain (mRS score 4 → 3)</td>
</tr>
<tr>
<td>R20</td>
<td>60/M</td>
<td>Cannot determine</td>
<td>Cannot determine</td>
<td>GAD Ab (+)</td>
<td>Conditioning effect</td>
<td>Doses held for 6 mo after PE; dose held; wearing-off effect</td>
<td>23</td>
<td>20</td>
<td>Decreased spasms and stiffness; decreased startle response and stiffness</td>
</tr>
<tr>
<td>R21</td>
<td>62/F</td>
<td>Cannot determine</td>
<td>Cannot determine</td>
<td>GAD Ab (+)</td>
<td>Conditioning effect</td>
<td>Wearing-off effect; decreased frequency due to insurance; decreased dose</td>
<td>216</td>
<td>205</td>
<td>Improved mobility; decreased spasms and stiffness</td>
</tr>
<tr>
<td>R22</td>
<td>72/F</td>
<td>3</td>
<td>3</td>
<td>GAD Ab (+)</td>
<td>Discontinued prematurely</td>
<td>N/A</td>
<td>48</td>
<td>N/A</td>
<td>Improved gait; decreased spasms and stiffness</td>
</tr>
<tr>
<td>R23</td>
<td>68/F</td>
<td>5</td>
<td>8</td>
<td>GAD Ab (-)</td>
<td>Decreasing benefit over time; discontinued prematurely</td>
<td>Wearing-off effect; dose held</td>
<td>12</td>
<td>N/A</td>
<td>Improved balance, walking speed, and posture; decreased startle response and spasms</td>
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<tr>
<td>R24</td>
<td>61/F</td>
<td>0</td>
<td>1</td>
<td>GAD Ab (+)</td>
<td>Discontinued prematurely</td>
<td>Dose held</td>
<td>11</td>
<td>N/A</td>
<td>Improved gait; decreased stiffness (mRS score 4 → 3)</td>
</tr>
</tbody>
</table>

Abbreviations: IVIg = intravenous immunoglobulin; mRS = modified Rankin Scale; N/A = not applicable; SPS = stiff-person syndrome.
for at least 3 months, as in our original IVIg trial.7 The subsequent maintenance IVIg doses either remained the same (2 g/kg per month) throughout the follow-up period or varied from 1 to 2 g/kg every 3–6 weeks based on the results of dependency tests, as per standard IVIg maintenance protocol for all neurologic disorders.8

Data Availability
Data not provided in the article due to space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating the results.

Standard Protocol Approvals, Registrations, and Patient Consents
Chart review and data analysis were approved by the IRB of the Jefferson Office of Human Research (MCD: principal investigator). Patient consent was not required for this retrospective chart review.

Results
Demographics
The study included 36 patients, 29 women and 7 men, of median age 58 years (range 32–81 years). Time from symptom onset to SPS diagnosis ranged from 0 years (diagnosed the same year as symptom onset) to 26 years, with a median of 3.5 years. Time from symptom onset to treatment with IVIg ranged from 0 years (treated the same year as symptom onset) to 26 years with a median of 4 years. Thirty-two of the 36 patients were positive for GAD-65 antibodies with high titers, as previously specified14,14–16; 4 patients were diagnosed with seronegative SPS based on all the other required criteria and exclusions4,5 (Table 1, eTable 1, links.lww.com/NXI/A732). Five GAD-positive patients also had cerebellar involvement, as part of GAD-SPS spectrum disorder.5,17

Overall Clinical Changes and Benefits From IVIg
Of the 36 patients, 24 (67%) had a clinically significant response to treatment with IVIg, similar to what was noted in our original short-term (3-month) controlled study,7 with benefit extended up to a median period of 40 months (Figure 1). Of the 4 patients with seronegative SPS, 2 improved with IVIg; 1 had complications and discontinued treatment after a single dose, and the fourth did not respond to IVIg. Subjectively, the responders reported the following overall long-term experience with IVIg: improved gait, improved daily functioning, improved balance, decreased dysarthria and faster speech, decreased stiffness, decreased painful spasms, improved energy, decreased startle response, improved posture, and improved facial expression (Table 1). Based on objective neurologic examinations, responders were noted to have decreased rigidity, improved gait, improved facial expression, decreased nystagmus, and decreased dysarthria (in the patients with SPS and cerebellar findings).

Among the 36 patients who received IVIg, 12 patients did not exhibit any benefit (as defined above), at any time during a median of 3 months (range 1–24 months) of IVIg treatment (Figure 1; eTable 1, links.lww.com/NXI/A732). No differences in the clinical phenotype, GAD Ab status, or symptomatology characteristics were noted between the responders and nonresponders.

Response Assessed by the Modified Rankin Scale Score
Of the 24 IVIg responders, 8 patients (33%) responded to the extent that their modified Rankin Scale score improved by 1 point (in 6 patients) or by 2 points (in 2 patients), most dramatically illustrated by the ability to walk without an assistive device after treatment. Specifically, 6 of these patients were using a wheelchair before starting IVIg but became able to walk independently (R2 and R16; Table 1) or with a cane

Figure 1
Median Duration and Range of IVIg Treatment in 36 Patients With Stiff-Person Syndrome Categorized as IVIg Responders or Nonresponders

IVIg responders were subcategorized based on their response to long-term treatment—continued benefit over time, decreasing benefit over time, demonstration of a conditioning effect, not assessed with a dependency trial, or unable to assess due to premature discontinuation of therapy.
or walker (R5, R11, R19, and R24; Table 1) several months after IVIg; 2 others who required a cane or a walker to walk pre-IVIg became able to walk without assistance after several IVIg courses (R4, R10; Table 1). The other 16 responders maintained the same mRS score after long-term IVIg treatments, demonstrating a stabilizing effect.

Duration of Long-term Benefit of IVIg and Dependency Tests
For the 24 IVIg responders, the duration of treatment ranged from 11 to 216 months, with a median of 40 months (Figure 1). Sixteen of the 24 responders underwent formal dependency trials or an equivalent. After holding their IVIg infusions, reducing the monthly IVIg dose from 2 g/kg to 1 g/kg or prolonging the frequency of the infusions, there was a clear symptom recurrence indicating that maintenance therapy was beneficial and still needed. One patient (R1; Table 1) who declined further when IVIg was held due to poor venous access exhibited a satisfactory clinical response with less side effects when switched to SCIg; in this patient, SCIg continues to ensure improvement and stability for the last 2 years. Eight of the 24 responders continued receiving treatment without undergoing a formal dependency test (Figure 2); 2 of these patients continued to experience clear benefit and were categorized in Table 1 in the responders with continued benefit subgroup; another prematurely discontinued therapy because of medical comorbidities and was categorized in Table 1 in the discontinued prematurely subgroup; the remaining 5 continued on IVIg for a median of 58 months (range 13–143 months) because it was felt to be beneficial and were categorized in Table 1 in the responders with no dependency trial subgroup.

Subgroup Analysis of Long-term Responders Based on Continuing Stability, Declined Benefit, Conditioning Effect, or Safety Issues
Of the 24 patients who benefited from IVIg, 3 patients (12.5%) prematurely discontinued treatment after a median period of 12 months (range 11–48 months) due to other medical comorbidities (Figures 1 and 2). One patient discontinued IVIg due to cardiac risk factors, another due to starting other immunotherapies for rheumatologic conditions, and the third as advised due to a prior intracerebral hemorrhage considered unrelated to IVIg. Overall, other than the common and mild infusion–related reactions, no major adverse events were observed with the chronic IVIg treatments.

GAD-Positive Patients With SPS With Cerebellar Involvement (GAD-SPS Spectrum)
Five GAD-positive patients with SPS also had cerebellar findings with ataxia and dysarthria, consistent with GAD-SD.3,5,10 Three of these patients (R7, R11, and R13; Table 1) exhibited a beneficial response to IVIg with objective improvement in speech, balance, and nystagmus but with meaningful benefit for a median duration of 40 months (range 13–62 months) (Figure 1). Seven other patients (29.1%) also exhibited clinically meaningful improvement based on dependency trials for a median of 39 months (range 16–121 months), but started to notice a decreasing relative treatment benefit after an estimated median of 31 months (range 19–50 months), despite receiving high-dose IVIg treatments (Figure 2 and Table 1).

Three of the 24 responders (12.5%) (Figure 2) who initially demonstrated clear benefit experienced decreasing benefit over time but were continued on maintenance therapy despite a lack of objective decline with dependency tests. These patients requested continuation of IVIg therapy, citing increased fatigue and pain without treatment and expressing fear that their functional status would decline if not continued on maintenance therapy, exhibiting a form of conditioning effect.8,9 This patient subgroup remained on maintenance therapy for a median duration of 58 months (range 23–216 months) (Figure 2).

Of the 24 patients who benefited from IVIg, 3 patients (12.5%) prematurely discontinued treatment after a median period of 12 months (range 11–48 months) due to other medical comorbidities (Figures 1 and 2). One patient discontinued IVIg due to cardiac risk factors, another due to starting other immunotherapies for rheumatologic conditions, and the third as advised due to a prior intracerebral hemorrhage considered unrelated to IVIg. Overall, other than the common and mild infusion–related reactions, no major adverse events were observed with the chronic IVIg treatments.
decreasing benefit over time. One patient (R11, Table 1) had a substantial response with improvement in the mRS score, going from being a wheelchair user before IVIg to being able to walk with a walker after IVIg; he gradually exhibited, however, decreasing benefit and switched to rituximab. Two other patients (NR3 and NR8; eTable 1, links.lww.com/NXI/A732) did not show convincing signs of improvement and were categorized as nonresponders, although 1 patient noted a mild but transient improvement in gait.

Discussion

The study demonstrates that maintenance therapy with IVIg continues to be effective over a median of 3.3 years in 67% of patients with typical SPS, improving daily functioning, gait, balance, painful spasms, posture, and facial expression with a demonstrable effect in decreasing stiffness, spasms and startle response. Although uncontrolled due to disease rarity and clinical ethics to give placebo over 2–3 years, this is a long-term study in a large group of patients with SPS seen over time by the same experienced clinicians that documents continued IVIg efficacy based on a combination of mRS scores, dependency tests, and objective clinical observations. The results complement the conclusions from the original short-term 3-month controlled study that the same investigators conducted 20 years ago with a much smaller number of enrolled patients. The present analysis, however, highlights several additional observations of increased clinical and practical importance.

First, 33% of responders experienced improvement in their main disabling symptoms over time substantial enough to improve their mRS score by 1 or 2 points; patients who were using a wheelchair or unable to ambulate independently before receiving IVIg became able to walk with an assistive device or independently with maintenance therapy. This demonstrates that a subset of patients can achieve and maintain major functional improvement with monthly IVIg. Given that in a longitudinal study patients with SPS manifested disabling progression over a 2–4-year observational period, the present data show that maintenance IVIg therapy provides a stabilizing effect and may delay disease progression.

Second, among all IVIg responders, 25% continued to experience persistent benefit for a median period of 40 months (range 13–62 months); 29.1% of them, however, started to experience diminishing relative benefit after an estimated median period of 31 months. Such a declining efficacy was not related to prolonged infusion frequency or reduced IVIg dosing, given that patients continued on a high dose of 2 g/kg per month as determined by the dependency tests, but it rather represents reduced effect most likely due to disease progression. As stated earlier, the longitudinal study with 57 GAD-positive patients with SPS examined and followed at the NIH every 6 months for a 2-year period by the same clinicians as in this study had shown that SPS is a progressive disease; 80% lost the ability to walk independently after a 2-year follow-up period without immunotherapy, exhibiting increased stiffness and heightened sensitivity scores, worsening functional status, higher frequency of falls, and impaired ability to walk independently or perform work duties. Importantly, after the first two-year follow-up period, 5 patients could no longer function with only antispasmodic therapy and required intermittent IVIg infusions with considerable benefit. On this basis, the present study suggests that IVIg may inhibit disability progression for a period of time in a considerable subset of patients with SPS, but the observation that 33% of patients did not respond and that 29.1% exhibited decreasing benefit over time highlights the need for more effective maintenance therapies, especially at the time when the benefit of IVIg starts to decline.

Third, a small (12.5%) patient subset with demonstrable initial improvement felt the need to continue on maintenance IVIg for a median of 58-month observational period, despite acknowledging no significant objective difference with dependency tests. These patients asserted that IVIg was helpful in reducing fatigue and pain, while expressing fear that they would decline if not continued on maintenance therapy. Such a conditioning effect, initially observed in patients with CIDP receiving maintenance IVIg therapy, has now been observed in patients with other autoimmune neurologic conditions on chronic IVIg therapy. In the 2 large controlled CIDP trials, ICE and PATH, 37% of patients randomized to placebo remained stable for a 24-week study period, even if they were previously observed to be IVIg-dependent. Because a placebo effect has been also noted in our randomized trial on patients with SPS receiving rituximab, a placebo component cannot be excluded among the small number of those patients in the present study who exhibited benefit but did not undergo dependency trials. Carefully performing periodic dependency trials in patients with SPS receiving chronic IVIg therapy remains fundamental to avoid overuse; furthermore, educating patients from the outset of potential risks is essential, especially in poorly mobilized patients with SPS with other comorbidities, such as insulin-dependent diabetes who are at risk for thrombosis and other adverse effects. The observation that 33% of patients who did not respond to IVIg during the first 3 months did not also respond even when therapy continued for up to 20 months underscores the need for prudent use of IVIg in clinical practice to avoid overuse.

Fourth, long-term high-dose IVIg tolerance was very good with only 3 of the 24 responders discontinuing therapy prematurely due to IVIg-related side effects or other medical comorbidities. Two of the nonresponders also had IVIg-related side effects or medical comorbidities preventing continued use.

Despite some study limitations, mainly the lack of a control group due to obvious difficulties in giving placebo for long periods in a rare disease and the constraints of a retrospective chart review, this study has conclusively demonstrated the effectiveness of IVIg as chronic maintenance therapy while highlighting the need for new or novel therapies for the chronic management of SPS. Promising immunotherapies should be, however, tested in a randomized controlled design, as done with the rituximab trial, but in a larger number of patients involving many centers, or as concluded from the results of the large but uncontrolled hematopoietic stem cell transplantation
study that led to early termination.\textsuperscript{18,19} Although both of these studies failed to show efficacy, rituximab and autologous hematopoietic stem cell transplantation can still provide benefit in some patients with SPS over a long time period.\textsuperscript{10,20,21}

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**Disclosure**

None to report. Go to Neurology.org/NN for full disclosures.

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**References**


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<table>
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Jessica Yi and Marinos C. Dalakas

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