Therapies in Stiff-Person Syndrome
Advances and Future Prospects Based on Disease Pathophysiology

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Abstract

Among the glutamic acid decarboxylase (GAD)-antibody–spectrum disorders, the most common phenotypic subset is the stiff-person syndrome (SPS), caused by impaired GABAergic inhibitory neurotransmission and autoimmunity characterized by very high titers of GAD antibodies and increased GAD-IgG intrathecal synthesis. If not properly treated or untreated because of delayed diagnosis, SPS progresses leading to disability; it is therefore fundamental to apply the best therapeutic schemes from the outset. This article is focused on the rationale of specific therapeutic strategies based on the SPS pathophysiology targeting both the impaired reciprocal GABAergic inhibition to symptomatically improve the main clinical manifestations of stiffness in the truncal and proximal limb muscles, gait dysfunction, and episodic painful muscle spasms and the autoimmunity to enhance improvement and slow down disease progression. A practical, step-by-step therapeutic approach is provided, highlighting the importance of combination therapies with the preferred gamma-aminobutyric acid–enhancing antispasmodic drugs, such as baclofen, tizanidine, benzodiazepines, and gabapentin, that provide the first-line symptomatic therapy, while detailing the application of current immunotherapies with intravenous immunoglobulin (IVIg) plasmapheresis, and rituximab. The pitfalls and concerns of long-term therapies in different age groups, including children, women planning pregnancy, and especially the elderly considering their comorbidities are emphasized, also highlighting the challenges in distinguishing the conditioning effects or expectations of chronically applied therapies from objective meaningful clinical benefits. Finally, the need for future targeted immunotherapeutic options based on disease immunopathogenesis and the biologic basis of autoimmune hyperexcitability are discussed, pointing out the unique challenges in the design of future controlled clinical trials especially in quantifying the extend and severity of stiffness, episodic or startle-triggered muscle spasms, task-specific phobias, and excitability.
Stiff-person syndrome (SPS) is an autoimmune disorder due to impaired inhibitory GABAergic neurotransmission associated with high-titer antibodies against glutamic acid decarboxylase (GAD), the enzyme that catalyzes the synthesis of the inhibitory gamma-aminobutyric acid (GABA). Approximately 5–10% of patients with SPS also have cerebellar ataxia, epilepsy, or nystagmus and comprise part of the GAD-antibody–spectrum disorders (GAD-SD), that also include autoimmune epilepsy, cerebellar ataxia, limbic encephalitis, and myoclonus. SPS-SD is a potentially treatable group of autoimmune diseases that all have in common GAD-antibody–associated neuronal excitability. Among all the SPS-SD, however, SPS is the most common and the most challenging because it presents slowly with a complex symptomatology that delays diagnosis and treatment. This is especially important because SPS is a steadily progressive disease with unique pathogenesis, highlighted by impaired reciprocal inhibitory GABAergic neurotransmission and autoimmunity that require a combination of specific long-term therapeutic schemes from the outset. The autoimmunity against inhibitory neurotransmission in SPS-SD is enhanced by the presence of other synaptic antibodies, as discussed later, including antibodies against glycine-a1 receptor and those against amphiphysin and gephyrin seen in paraneoplastic SPS.

The purpose of this article was to outline the rationale and merits of the various therapeutic strategies and discuss how best to improve patients’ outcome and design new trials. More specifically, it is aimed to (1) provide practical, step-by-step therapeutic approaches based on pathogenic mechanisms, stressing the need for early therapy initiation to maximize the control of stiffness and spasms without excessive sedation and prevent disease progression and disability; (2) address the importance of combined therapies targeting the 2 main disease pathomechanisms responsible for the patients’ symptoms, namely, the consequences of impaired GABAergic reciprocal inhibition that results in muscle stiffness, spasms, and gait dysfunction and the rationale for applying immunotherapies; (3) describe how best to initiate early immunotherapy while stressing the concerns connected with chronic maintenance therapies; (4) highlight the therapeutic challenges in different age groups, including pediatric SPS, women planning pregnancies, and the very late-onset SPS in the elderly; and (5) outline the challenges in the design of clinical trials and the potential of new targeted immunotherapies as the neuroimmunology field is now advancing.

The Rationale of Therapeutic Strategies in Patients With SPS and the Challenges of Early Diagnosis

The diagnosis of SPS, according to accepted diagnostic criteria as of 20011,6 and currently evolved, is based on the combination of (1) stiffness of the axial and proximal muscles, most prominently in the abdominal and thoracolumbar paraspinals, leading to hyperlordosis, difficulty turning and bending, a slow freezing gait, and uncontrolled falls; (2) superimposed, often painful, muscle spasms triggered by anxiety, task-specific phobias, and excessive startles from unexpected auditory, visual, or tactile stimuli; (3) electromyographic signs of motor unit activity at rest concurrently from agonist and antagonist muscles and in spite of relaxation efforts; (4) very high GAD-antibody titers in the serum (>10,000 IU/mL by enzyme-linked immunosorbent assay) or detection of GAD antibodies in the CSF6; and (5) the absence of other neurologic signs that may point out an alternative diagnosis. In approximately 20% of patients with undetectable or very low GAD-antibody titers, the diagnosis may be challenging requiring the exclusion of functional neurologic disorders and adherence to the strict clinical and neurophysiologic criteria outlined above. Although in such patients, an empirical trial with diazepam for relieve of spasms and stiffness is sometimes used in aiding the diagnosis, this effort does not strengthen the diagnostic accuracy because a positive effect of diazepam cannot distinguish an organic from a functional disorder.

The therapies in SPS are aimed at the 2 main pathogenic mechanisms: (1) impaired reciprocal GABAergic inhibition, the key neurophysiologic dysfunction causing stiffness and spasms, that justifies the need for GABA-enhancing therapies, and (2) autoimmunity, based on SPS autoimmune pathogenesis, that justifies the application of immunotherapies.1-10

The Need to Therapeutically Target the Impaired Reciprocal GABAergic Inhibition

Reciprocal inhibition is a fundamental process of our normal physiology ensuring, when one muscle (i.e., the biceps) contracts, the automatic relaxation of its antagonist muscle (i.e., the triceps). This process occurs because when the alpha motor neurons send messages to the agonist muscles to contract, the gamma neurons of its antagonist’s muscle do not discharge, being silenced by the inhibitory GABA interneurons (Figure 1, A and B), as described more than 20 years ago.
with detailed electrophysiologic studies and has been recently elaborated diagrammatically. In SPS, these inhibitory GABAergic signals are inhibited allowing the gamma motor neurons to fire uncontrollably resulting in the motor unit firing at rest concurrently by the agonists and antagonists, in spite of muscle relaxation, because of failing to silence the antagonist muscle when its agonist contracts (Figure 1C). Such a continuous motor unit activity is clinically expressed as muscle stiffness and painful muscle spasms due to concurrent contraction of agonist and antagonist muscles, as seen in typical patients (Figure 2).

The impaired GABAergic inhibitory neurotransmission in patients with SPS has been supported and explained by the following fundamental observations: (1) reduction of brain GABA, shown by magnetic resonance spectroscopy studies; (2) concomitant reduction of GABA levels in the CSF; and (3) dysfunction of supraspinal GABAergic neurons resulting in motor cortex hyperexcitability, based on transcranial magnetic stimulation studies, that explain the stimuli-induced muscle rigidity and spasms. GABA, being the predominant inhibitory neurotransmitter in the brain with 25–35% of synapses being GABAergic, is involved in muscle tone, fear, anxiety, autonomic responses, and epileptogenesis, all symptoms seen in SPS. The consequences of the impaired reciprocal GABAergic inhibition and cortical hyperexcitability are clinically expressed by the following 4 critical SPS symptoms we aim to target with the GABA-enhancing drugs:

1. Stiffness of the truncal and proximal limb muscles, prominent in the thoracolumbar paraspinals and abdominal muscles, causing difficulty turning and bending forward, hyperlordotic posture, and increased thoracolumbar curvature, which in chronic and severe cases, can be associated with hypertrophy of the lumbar paraspinals or resembles an S-shape thoracolumbar spine formation, as depicted in the X-rays (Figure 2, A–D).

2. Gait dysfunction and falls, causing slow walking, with a “freezing” or “statue”-like appearance, and unexpected falls due to startle response by various external stimuli or when anticipating physically challenging conditions. As the disease worsens and the stiffness becomes more severe, patients cannot walk independently requiring aids or becoming wheelchair-bound.

3. Superimposed episodic painful muscle spasms in the trunk, face, or extremities. Muscle spasms can be precipitated by unexpected auditory or tactile stimuli, such as a phone-ring, sirens, sudden touches, situational phobias, or conditions triggering anxiety and emotional stress. If occur frequently or seem unusual and unexplained, they may be clinically viewed as representing a functional or a primary anxiety disorder leading to psychiatric evaluations. The episodic nature of spasms is important when assessing response to therapies because they may not be evident when a patient is seen in the clinic; most importantly, their frequency and severity throughout the day or the week need to be considered and counted when assessing response to therapies especially in formal clinical trials. For these reasons, we ask the patients and their family to keep a diary recording their occurrence along with the number of falls or startle responses. In severe cases, the spasms and stiffness in the thoracolumbar, thoracocervical, sternal, and laryngopharyngeal muscles become continuous causing breathing difficulties, tremulous voice with difficulty verbalizing, hyperhidrosis, and tachycardia, a condition we have called “status spasticus” that often requires intervention with IV diazepam.

4. Task-specific phobias associated with anxiety and emotional upset, especially fear in initiating or completing a walking task, resulting in freezing, intense spasms, and falls. Phobias are frequent in patients with SPS when walking among crowds, such as in airports, malls, or eateries; crossing a street due to anxiety to make it during the duration of the green light; thinking of going down steps or taking escalators; and generally being in unfamiliar or stressful environments, triggering freezing spasms that prevent them from going out alone. It is important to stress that patients with SPS do not have a history of psychiatric symptoms, phobic neurosis, or signs of somatizations several years before the manifestation of SPS.

The Need and Rationale for Immunotherapies to Target SPS Autoimmunity

The evidence that SPS is an autoimmune process is overwhelming, although the exact autoimmune pathomechanisms remain still obscure because pathogenic antibodies or T-cell-targeted–specific antigens have not yet been identified. The evidence of SPS autoimmunity is based on the following:

1. The serum and CSF of patients with SPS immunoreact with GABAergic neurons on rat cerebellum recognizing recombinant GAD65; (2) intrathecal production of GAD65 antibodies indicative of clonal B-cell activation within the CNS along with the reduction of CSF GABA level suggesting impaired GABA synthesis; (3) oligoclonal IgG bands, detected in the CSF of 67% of our patients, and increased GAD65-specific IgG index in 85% of them; (4) antibodies to other GABAergic or inhibitory synaptic antigens in the patients’ serum and CSF directed against GABA–receptor–associated protein (anti-GABARAP) found in 70% of the patients; (5) glycine-a1 receptor (anti-GlyR) seen in 10%–12% of patients with SPS and amphiphysin, seen in about 5% or gephyrin seen in a single case. When SPS is a paraneoplastic manifestation (Figure 3), (6) GAD-reactive B cells in the peripheral blood and bone marrow with potential to differentiate into antibody-producing cells, suggesting that targeting memory B cells or plasma cells may be of therapeutic benefit; (6) cytotoxic T cells, reported in brain tissue biopsies from some GAD-positive patients with epilepsy, suggesting a potentially specific neurotoxic T-cell effect against GABAergic interneurons. CD4+ and CD4+ CD8+ T cells can also recognize GAD65-specific epitopes, while GAD65-specific T cells with Th1 and Th1/Th2 profiles have been produced intrathecally.
Furthermore, GAD65 is a major T-cell autoantigen in non-obese diabetic mice, and a T-cell response has been suggested in DM1; (7) strong association, in up to 80% of our patients, with alleles in the DR (DRb1 0301) and DQ (DQb1 0201) phenotypes1,2,4,6,8; (8) association with other autoimmune diseases, such as thyroiditis, DM1, pernicious anemia, or vitiligo2,4,25; and (9) high incidence of family autoimmunities especially GAD-associated DM1. In DM1, however, anti-GAD antibodies are of low titers and directed against conformational epitopes; by contrast, the GAD antibodies in SPS are in very high titers and always directed against linear epitopes.2,4,6,7

The aforementioned autoimmunities, although compelling, have also raised concerns mainly because all the antibodies, except for the anti–glycine-α1 receptor, target cytoplasmic antigens serving as good biomarkers but having uncertain pathogenicity. Furthermore, although high GAD-antibody titers matter in SPS diagnosis, no association exists between antibody titers and disease severity1,2,4,6 and no meaningful titer reduction has been observed in the controlled immunotherapy trials with intravenous immunoglobulin (IVIg) or rituximab.27,28 Based on these considerations, GAD antibodies presently remain markers of aberrantly activated innate and acquired immunity.2,4,10 On the other hand, the observations that in SPS, the GAD65 antibodies (1) are detected in the serum and CSF and they are associated with reduction of CSF GABA levels; (2) recognize the purified GAD antigen by the western blot; and (3) immunoreact with GABAergic neurons suggest that GAD antibodies may exert some functional, albeit still unproven, effects on their respective neurons.2,4 Most importantly from the therapeutic standpoint, the normal brain MRI imaging, in spite of the patients’ severe clinical disability, along with the magnetic resonance spectroscopy data, suggests a functioning blockade of the respective neurons rather than neuronal destruction, a notion that explains the reversibility of the clinical symptoms we witness after therapies while also highlights the need to consider early immunotherapy initiation before permanent neuronal damage takes place.2,4

![Figure 1 Reciprocal Inhibition and Its Electrophysiology](image)
Step-by-Step Therapies in SPS Based on Disease Pathophysiology

According to the above, a practical step-by-step therapeutic approach in patients with SPS is based on the following drugs and procedures either used alone or in combination (Table).

A. GABA-Enhancing Drugs
These are the first-line therapies because they improve GABAergic inhibitory neurotransmission, suppress cortical hyperexcitability, or increase CNS GABA exerting a positive effect on impaired reciprocal inhibition and improving the 4 fundamental SPS symptoms mentioned earlier. Their benefit has also been well delineated as first-line therapy in a large number of male veterans.29 No controlled studies have been, however, conducted or anticipated to be performed with these agents.

B. Immunotherapies
These should start as soon as the first-line therapies with GABA-enhancing drugs are not fully effective. Delays in immunotherapy initiation are not advisable because irreversible clinical manifestations or disease progression may take place, as shown in the longitudinal follow-up study.30

C. Combination of A and B
This is the most common and sensible therapeutic strategy because each one of the 2 therapeutic categories works differently: one targeting pathophysiology and the other autoimmunity.

Supportive Physical Therapies
Although not always needed, preferred, or tolerated, selective physiotherapy (such as aqua therapy, deep tissue massage, heat, or ultrasound therapy) may offer benefits to some patients at various stages of the disease. A few patients follow some nonpharmacologic stress release techniques including cognitive/behavioral therapies, yoga, or mediation, but the benefits are undocumented and the choice for such therapies is entirely individualized and pursued independently.

Role of Supportive Psychotherapies
Because several patients with SPS experience anxiety in public spaces and phobias of falling or completing physical tasks,
special understanding by their immediate environment or psychological support at home and at work is fundamental, especially because their symptoms are episodic and the beneficial effects of antispasmodic therapies not fully or consistently effective throughout the day. The patients’ phobias can lead to depression, while the painful spasms may, after a period, lead to pain clinic management or addiction to narcotics. The reported worsening of symptoms with serotonin-norepinephrine reuptake inhibitors, even if we have not observed it in our series, needs to also be taken into consideration. It is important to highlight that many patients with SPS have been exposed to long-term suffering and frustrations due to misdiagnoses or delayed diagnosis, while others have been diagnosed with a “functional neurologic disorder” going through unnecessary cognitive rehabilitation or treatment with psychiatric drugs without any direct benefit on their physical symptomatology. Accordingly, the neurologist’s support, understanding, and reassurance are needed from the outset.

To determine whether the patients’ anxiety and phobic symptoms precede stiffness and spasms or represent a reaction to disability, we have performed a detailed neuropsychological assessment in patients with SPS in collaboration with the psychiatry department of NIH (NIMH). This study revealed no evidence of psychopathology or neurocognitive dysfunction. In contrast to a previous study which had shown that patients with SPS had phobic neurosis believing that their fears are unrealistic, our study showed that the patients did not have premorbid phobias or neurocognitive impairment but perceived their fears and avoidance behavior as realistic caused by SPS rather than due to an inherent phobic neurosis, not meeting the criteria of DSM-IV. Considering that low GABA has been connected to anxiety disorders, this observation is important, and on this basis, we need to reassure the patients from the outset that if the disease improves with prompt initiation of combined therapies, their phobias will also improve, a

Figure 3 Antigenic Targets in the Inhibitory Synapses of Patients With SPS-SD

The targeted presynaptic antigens in SPS-SD are GAD (1), the enzyme that synthesizes GABA, and amphiphysin (2), a synaptic vesicle protein responsible for endocytosis of plasma membranes after GABA release. The postsynaptic targets are glycine receptor (3), a ligand-binding ion channel that allows the passage of chloride ions; gephyrin (4), a tubulin-binding protein needed for clustering both GABA-A and glycine receptors; and GABA-A receptor-associated protein (GABARAP) (5), a linker protein which promotes the organization of the GABAA receptors (2,4). Originally published in Dalakas M. Stiff-person Syndrome and GAD Antibody-spectrum Disorders: GABAergic Neuronal Excitability, Immunopathogenesis and Update on Antibody Therapies. Neurotherapeutics 2022;19:832. GABA = gamma-aminobutyric acid; GAD-SD = glutamic acid decarboxylase-spectrum disorders; SPS = stiff-person syndrome.
Table: Step-by-Step Therapeutic Approaches in SPS Based on Disease Pathophysiology

1. GABA-enhancing drugs
   a) GABA<sub>α</sub> receptor-binding benzodiazepines
      - Diazepam
      - Clonazepam
   b) Centrally acting antispasmodic drugs
      - Baclofen: GABA<sub>β</sub> receptor binding
      - Tizanidine: α2 adrenergic receptor agonist
   c) Antiepileptics, enhancing GABA and improving pain
      - Gabapentin that enhances GABA synthesis
      - Vigabatrin that inhibits GABA transaminase
      - Tiagabine that inhibits GABA reuptake
      - Levetiracetam that potentiates GABAergic transmission
      - Pregabalin (structurally similar to GABA but binds to VGCC)

2. Other, third line, antispasmodics (as adjunct agents if 1a, b, c options are not adequately effective)
   - Botulinum toxin: Only for focal spasms in selected patients
   - Methocarbamol (Robaxin)
   - Cyclobenzaprine (Flexeril)
   - Dantrolene

3. Immunotherapies
   a) IVIg
      - Start with 2 g/kg every mo for 3 mo
      - If no benefit after 3 mo, go to 2b
      - If benefit, proceed to IVIg maintenance with 1–2 g/kg every 4–6 wk with periodic dependency trials to confirm continuing benefit
   b) Rituximab
      - 2 g divided in 15 d
      - If clear benefit after 6 mo, repeat it every 6–12 mo (according to when there is a demonstrably declining benefit)
   c) Other
     - Plasmapheresis: As an adjunct short-term therapy for exacerbations of severe spasms
     - Autologous hematopoietic stem-cell transplantation (for a disabling, rapidly progressive disease, if all therapies failed to provide sufficient benefits)

4. Advisable step-by-step sequence: Combination of 1 (a, b, c) with either 3a, 3b, or 3c

5. Supportive therapies
Abbreviations: GABA = gamma-aminobutyric acid; IVIg = intravenous immunoglobulin; VGCC = voltage gated calcium channel.

recent report that SPS-SD patients have impaired verbal learning and recall fluency, attention, and processing speed<sup>35</sup> should be viewed with caution because it was based on a retrospective chart review of patients with SPS-SD, most of which did not have pure SPS but other comorbidities or neurologic impairments, for which they have been receiving variable combinations of benzodiazepines, antidepressants, antispasmodics, antiepileptics, and opioids.

### Categories of GABA-Enhancing Drugs

#### GABA<sub>α</sub> Receptor-Binding Drugs: Benzodiazepines (Diazepam or Clonazepam)
Diazepam or clonazepam provide transient help to most patients, but the high doses sometimes required cannot be tolerated because of somnolence, mood changes, and fatigue, especially in the elderly, while chronic use frequently leads to dependency. It is preferable, therefore, to start with low doses of diazepam, 5 mg BID, and if well tolerated increase it to 15 mg daily or up to 10 mg BID adding a third dose as needed. One should try to avoid higher doses, such as up to 50–60 mg daily, as had been used by some practitioners before the availability of immunotherapies. Clonazepam 0.5–5 mg is as effective and sometimes preferable to diazepam. Alprazolam, lorazepam, and temazepam are also used. Diazepam is especially effective in status asthmaticus, preferably given IV in severe and long-lasting spasms or in a rectal form. We are in the process of exploring in a pilot trial whether the intranasal diazepam spray (Valtoco) approved for seizure clusters<sup>34</sup> is as beneficial and preferable in these cases because of easy self-administration and better tolerance.

#### Centrally Acting GABA<sub>β</sub> Receptor Binding (Baclofen) and α2 Adrenergic Receptor Agonist (Tizanidine)
Baclofen, a direct agonist of the GABA<sub>β</sub> receptors not requiring endogenous GABA for synaptic inhibition, is a preferred choice among all GABA enhancers, starting with 10 mg daily increasing it slowly to 3 times daily. Higher doses, even up to 60 mg daily, can be used if helpful with monitoring for possible cognitive side effects. Tizanidine (2 mg 3 times daily) is a centrally acting α2 adrenergic receptor agonist that impairs the release of excitatory amino acid from spinal interneurons and inhibits interneuronal activity. Because it has additional antinociceptive effects, it is also helping the painful spasms.

A baclofen pump intrathecally has also been used in some patients with SPS to improve spasticity, but the results have been variable.<sup>35</sup> A semicontrolled study in 3 patients from Mayo clinic showed reduction of reflex EMG activity but clinical improvement in only one of the 3 cases.<sup>36</sup> We have not recommended such therapy to any of our patients but, based on patients referred to us with baclofen pumps already inserted, the beneficial effect is not overall impressive. On the contrary, since some patients with SPS also have insulin-dependent diabetes and use insulin pump or receive treatment with IVIg through either a port or subcutaneously, having another pump affects the daily quality of life, especially if the benefit is marginal. Furthermore, some reported life-
threatening intrathecal baclofen withdrawal symptoms, pump failures, and sepsis are of concern.

Antiepileptics That Enhance GABA Synthesis or Facilitate GABAergic Transmission

Gabapentin is tried in most of our patients because it enhances GABA synthesis and helps the painful spasms, starting with 300 mg TID and increasing the dose as tolerated. Other GABA-enhancing antiepileptics that may offer benefits, if well tolerated, include vigabatrin, which acts by inhibiting GABA transaminase; tiagabine, an inhibitor of GABA reuptake; and levetiracetam that facilitates the potentiation of GABAergic transmission (Table). Pregabalin, which structurally is similar to GABA, does not bind GABA but binds to voltage gated calcium channel; it helps the pain but not the spasms, and it is less preferable.

Other Antimuscle Spasm Agents: Methocarbamol (Robaxin), Cyclobenzaprine (Flexeril), Dantrolene, and Botulinum Toxin

Methocarbamol (Robaxin) at doses 1,000 mg QID can be helpful for painful spasms. It can also be given IM. Cyclobenzaprine (Flexeril) 10 mg TID has also been tried, but we do not use it because paradoxically it can cause worsening of the symptoms.

Botulinum toxin can be a useful agent for focal SPS providing significant relief in the injected areas. It may be considered for some patients with localized spasms or prominent painful spasms regionally in an accessible area (i.e., 1 leg in the stiff-leg syndrome, face in stiff-face syndrome) or certain muscle regions, such as the paracervical or lumbosacral paraspinals, if they continue to cause painful spasms in spite of the other therapies. The benefit is however selective and overall short-lived.

Dantrolene used for malignant hyperthermia binds to the ryanodine receptor and decreases intracellular calcium concentration blocking the release of calcium from the muscle sarcoplasmic reticulum. It can potentially reduce stiffness, but it is rarely used.

Collectively, the first choice of all antispasmodics is oral baclofen, combined with gabapentin and low doses of diazepam; the other aforementioned agents are reasonable alternatives if well tolerated.

Immunotherapies

If the GABA-enhancing agents do not offer a satisfactory benefit after 2–3 months and the patients are not fully functioning, one needs to proceed to immunotherapy. Although immunotherapy initiation should not be delayed in these patients because SPS can be a progressive disease, many patients due to delayed diagnosis have already accumulated some degree of disability when immunotherapy is started clouding the prospects of full-symptom resolution. The first preferred treatment is with IVIg which is the only immunotherapeutic drug with proven efficacy in a controlled study with excellent tolerance.

Intravenous Immunoglobulin

In a double-blind, placebo-controlled trial we conducted more than 20 years ago in GAD-positive patients with SPS, IVIg showed significant improvements in objective stiffness parameters based on validated quantitative scales, hyperexcitability scores, and activities of daily living. Patients experienced reduced stiffness, especially in the paraspinal muscles with more muscle flexibility; less falls; improvement in their gait becoming able to walk without assisted devices (Figure 4, A and B); and with substantial reduction of anxiety-triggered spasms becoming able to perform again most of
daily activity functions. In that trial, based on predefined criteria, the stiffness scores significantly decreased and the heightened-sensitivity scores were markedly reduced after 3 monthly IVIg infusions; the symptoms started, however, to rebound 4–6 weeks after the patients switched to placebo.27 This pivotal study has conclusively shown that after 3 monthly infusions, IVIg was effective in up to 75% of patients with SPS who were symptomatic with inadequate response to antispasmodic and GABA-enhancing drugs.27

In practice, IVIg is given in a monthly dose of 2 g/kg (based on the ideal-body weight), divided in 2–3 consecutive days taking into account the patient’s age, other comorbidities, and tolerance; if poor tolerance or allergic reaction is noticed to one brand of IVIg, it is prudent to try another company’s product.27,43 If there is benefit after each monthly IVIg infusion, IVIg is continued for 3–6 more consecutive months at the same dose. From there on, there is a need to assess maintenance schedule by either prolonging the monthly infusion intervals to every 5 or 6 weeks or reducing the minimum required dose from 2 to 1 g/kg by performing dependency trials, as explained below, to avoid overuse, considering the commonly seen conditioning effects with chronic IVIg therapy.43 Most of the patients may continue to require 2 g/kg but at somewhat longer monthly intervals.

Subcutaneous immunoglobulin may also be an option for maintenance therapy in those patients with poor venous access or systemic comorbidities such as history of thromboembolic events.43 Because subcutaneous immunoglobulin given weekly provides a steady-state serum IgG level, it is especially useful for those patients with an early wearing-off effect to ensure sustained benefit.43–45

Long-term Monthly Maintenance Therapy With IVIg

Since the positive-controlled trial of 2001, if IVIg is effective after the first 3 monthly infusions it is being continued as the preferred chronic maintenance therapy. The chronic use of IVIg has been, however, rather liberal and often overused, necessitating collection of long-term efficacy data and evidence that monthly maintenance therapy is justified in sustaining stability or arresting disease progression. Performing dependency trials is therefore essential considering that a conditioning effect is a common problem with chronic IVIG therapy due to fear that patients may worsen without it, even without exhibiting objective benefits.43 One study in 19 patients receiving IVIg therapy for 2–3 years showed chronic benefit based on retrospective data collection of patient-reported scoring system, but without objectively assessing continuing efficacy.46 These issues have been recently addressed in a large study of 36 GAD-positive patients with SPS diagnosed and treated with monthly maintenance IVIg by the same neurologists who determined the long-term effects of IVIg over a 10-year period based on improvement in mRS scores, physician-assessed stiffness, balance, and gait.47 Continuing benefit was objectively assessed based on performing dependency trials evaluating symptom recurrence after stopping IVIg, prolonging infusion frequency, decreasing monthly dose, or wearing-off effects in-between doses. In this large cohort, 24 of the 36 patients (67%) had a clinically meaningful response over a median 3.3 (range 1–18) year period exhibiting improved gait, posture, and balance and also decreased stiffness, spasms, and startle response; some wheelchair-bound patients and those ambulating with devices walked unassisted.47 Among the responders, 37.5% had long-term stability without disease progression for 4.3 (range 1–18) year period; the other 29.1%, however, although continued to experience improvement, they also exhibited diminishing benefits after a mean 3.3 year period due to disease progression highlighting the need for more effective long-term therapies.47 Of interest, 12.5% exhibited a conditioning effect after 5 (range 2–18) years emphasizing the need to perform periodic dependency tests during chronic therapy to avoid overuse, as stressed in other neurologic disorders on chronic IVIG therapy.43

Based on these 2 large short-term and long-term studies, IVIg is effective in SPS and remains a key immunomodulatory therapy with proven benefit requiring, however, a judicious use for chronic maintenance to avoid overuse and conditioning effects. Accordingly, we advise to (1) stop IVIg if after the first 3 monthly infusions, there is no objective benefit; (2) continue with 1–2 g/kg monthly infusions, if there is a clearly objective improvement and good tolerance after the first 3 months; (3) perform periodic dependency tests by either reducing the total monthly IVIg dose (from 2 to 1 g/kg) or prolonging infusion intervals (from 4 weeks to 5 or 6) to objectively assess for signs of regression in the frequency and severity of spasms, gait, and stiffness (preferably documented in a daily diary) to determine the need to continue at the most beneficial dose; and (4) if no objective worsening is documented during the dependency trials, may stop IVIg for a few months to assess worsening before its continuation is justified.

Rituximab

If the benefit of IVIg is not sufficient after 3 months or it is poorly tolerated, one may consider to proceed to rituximab which anecdotally had been promising.48 In the largest placebo-controlled trial we performed in 24 patients with SPS, using the same scales as we used in the effective IVIg controlled study, no statistically significant benefit of rituximab compared to placebo was demonstrated because of a strong placebo effect.28 In spite of lack of statistically significant data, however, 7 patients (58%) objectively improved in all clinical parameters, while 4 of them (33%) who had severe disease exhibited dramatic improvements from using 2 canes to being able to walk unassisted or even go skiing, as shown for one of these patients (Figure 4, C and D).28 We retrospectively identified that one reason contributing to the statistically negative data and placebo effects might have been the inclusion of some patients with not clinically severe disease because in such patients, the scales are not sensitive enough to capture small changes. The argument that this was a small series and a 6-month study period was not sufficient to capture benefit is not correct because this was the
largest controlled study, and like most trials with rituximab in other neurologic diseases, the benefit is always seen after the first 6 months but needs subsequent infusions for maintenance. On this basis, rituximab is a very liable option for a subset of patients with significant symptoms (benefiting close to half of them in the large controlled study), who do not sufficiently respond to IVIg and the GABA-enhancing drugs.

Follow-up Maintenance Rituximab Infusions

In contrast to anti-CD20 agents used every 6 months in patients with relapsing MS who may develop new lesions or relapses, in patients with SPS who improved after the first 6 months, the follow-up infusions are not necessarily needed every 6 months based on a number of patients we follow, but often much longer. If the improved patients remain stable, one can wait for early signs of worsening, which in most patients can be seen after 8–12 months and in some others even later. For occasional patients, however, who regress earlier than 6 months, we find it preferable to use 1 g every 3 months to ensure stability instead of 2 g every 6–12 months. The need for retreatment should also not be based on GAD-antibody titers because they do not predict improvement nor do they correlate with disease severity based on the controlled trial where the antibody titers were reduced but not to a statistically significant level. It is important however to follow the immunoglobulin levels every 3–6 months, being careful not to reinfuse patients with serum IgG substantially below normal to prevent susceptibility to infections especially during the COVID-19 pandemic. Although the CD27+ memory B cells may be a helpful biomarker to follow based on experience with other antibody-mediated autoimmunities because their reappearance correlates with disease worsening, their value in SPS remains unexplored.

Plasmapheresis

Plasmapheresis may be a viable option as an adjunct therapy for severe disease exacerbations based on a small case series. It offers however transient and overall limited benefits without evidence of long-term effects on disease progression to justify its use as chronic therapy. Because it also requires a hospital set-up or special units, it is not routinely used. The American Society for Apheresis guidelines, based on a recent case series of 344 patients where plasmapheresis was used as an adjunct to immunotherapies, did not make a strong recommendation for SPS, rating it as Grade 2C category III because the benefit was partial and observed in half of the treated patients.

Autologous Hematopoietic Stem-Cell Transplantation

A few patients with severe SPS who failed the aforementioned and other conventional immunotherapies have been treated with autologous hematopoietic stem-cell transplantation (auto-HSCT), but the results have been variable. In one study, 3 patients with SPS and 1 with progressive encephalomyelitis with rigidity and myoclonus who received auto-HSCT preceded by cyclophosphamide 2 g/m², granulocyte colony-stimulating factor, and antithymocyte globulin exhibited improved ambulation and ability to perform physical tasks; one wheelchair-bound patient became able to walk with a walker. A large study, however, aiming at 40 patients with SPS was terminated early after enrolling only 23 patients because of the lack of efficacy or minimal and transient benefits in conjunction with potential serious complications. One of the main limitations of that study, as pointed out, was the recruitment of patients with advanced disease and no objective measurements or validated scales used to quantify stiffness and spasms. Whether a controlled HSCT trial should be considered in patients with SPS with early disease unresponsive to immunotherapies remains to be determined. At this point, auto-HSCT is considered as an extreme remedy and the last option for those patients with SPS who remain refractory to conventional immunotherapies or exhibit a rapidly progressive disease and none of the new options described later is deemed appropriate.

Other Partially Effective or Failed Immunotherapies

Corticosteroids have been surprisingly of limited benefit based on our experience, while the possibility of triggering or exacerbating diabetes on long-term use in a chronic disease as SPS is a serious consideration because poorly controlled diabetes seems to worsen the SPS symptomatology. Although IV steroids are routinely used in GAD-associated encephalitis, they have been disappointing when tried in the acute spastic state (status spasticus) in SPS patients. Oral immunosuppressive agents, including azathioprine, methotrexate, cyclophosphamide, or mycophenolate mofetil, routinely used as maintenance therapy in other autoimmune neuromuscular diseases, have also been disappointing in SPS, in spite of rare case reports.

Therapeutic Challenges in Pediatric-Onset SPS, the Very Late-Onset SPS (SPS in the Elderly), and Women Planning Pregnancy

SPS can be seen in all ages. Although rare in children, there are several reported cases that require special attention in reference to applied therapies especially with the use of GABA receptor-binding drugs due to poor tolerance. The excessive drowsiness caused by diazepam and clonazepam may interfere with learning and school attendance which is additionally challenging because of phobias of these patients in public spaces. The same applies to the other GABA enhancers, with the better tolerated ones being low doses of baclofen and gabapentin. Due to these limitations, early IVIG initiation therapy along with supportive therapies is highly advisable. Pediatric psychotherapy support, special nonpublic schooling to enhance education for short periods, if considered essential, and the need to avoid as best as possible...
bracing or wheelchair confinement not to affect growth are essential from the outset.

For women planning pregnancy or in early pregnancy, it is highly advisable to start IVIG as early as possible to improve function and avoid any potential effects of GABA enhancers to the fetus. There is evidence, however, that SPS symptomatology improves during pregnancy but worsens after delivery in a pattern similar to the one seen in patients with MS, suggesting that the immunomodulatory shifts occurring during pregnancy may also apply to SPS and influence clinical symptoms. In a series of 9 pregnant women with SPS, symptomatic antispasmodic medications were significantly reduced in 5 of them with stabilization or improvement of their symptoms through the end of pregnancy, while all 9 women delivered healthy babies.

The most challenging therapies are however in the elderly because of comorbidities. In our experience with more than 10 GAD-positive patients aged 70 years or older, the most concerning issues are diabetes, poor venous access, and poor tolerance to GABA enhancers causing significant sedation. It is also very concerning that in this age group, the disease is more often misdiagnosed for cervical or lumbosacral radiculopathies and several of our patients have had prior laminectomies and fusions with significant cumulative disabilities. As a result, these patients may have worse prognosis due to incomplete or poor response and lesser tolerance to immunotherapies. There is therefore a need to increase awareness among practicing neurologists that SPS can start late in life (very late-onset SPS) requiring special attention to available therapies due to various comorbidities. Poor venous access, prior vascular disease, pulmonary emboli, and anticoagulants have been common issues in our patients when considering immunotherapies, especially IVIG.

Challenges on Therapies and Future Trial Designs in SPS

The goals of therapy in SPS should focus from the outset on maximizing the control of stiffness and spasms and improve gait, daily activities, and quality of life but without excessive sedation as observed with antispasmodics. Because of the highly subjective nature of some symptoms and the emotional charge connected with the painful spastic attacks that occur often but unexpectedly form sudden stimuli, there is a need to document effectiveness of therapeutic interventions with objective means. Asking the patients to keep a diary, recording the frequency and severity of spasms, the degree of pain associated with them, the number of falls or startle responses, and any changes in ambulation, mobility, or daily activities has been very helpful.

Since SPS is not as rare as believed, it is essential to increase awareness to start early immunotherapies and conduct large-scale controlled studies. The experience with long-term IVIG therapy has identified the need for more effective long-term therapies because IVIg—although still beneficial—cannot arrest disease progression in 30% of the patients after a mean period of 4 years. There are arguably challenges in a future study design because in addition to the standard scales of Activities of Daily Living and “time to walk” as used in other autoimmune neurologic diseases, in SPS there is a need to include methods that statistically capture the frequency and severity of episodic spasms and stiffness and the task-specific phobias. The lack of objective laboratory studies of response to therapies, such as MRI imaging as used in patients with MS, is also a major issue because efficacy is essentially based on clinical assessments. Taking into account the steady and complex symptom progression and the significant disability of some of the patients with SPS develop over time, there is a need to select patients with early but significant disease to evaluate efficacy because we learnt from the HSCT study which showed that selecting patients with very advanced disease may be difficult to show improvement. On the other hand, our experience with the rituximab trial has also shown that enrolling patients with mild disease may increase the chances of placebo effect because the clinical scales may not be sensitive enough to objectively capture fluctuating efficiencies to convincingly conclude on long-term benefits especially in small-scale enrollments. All these difficulties can now be overcome with more centers seeing patients with SPS, more experienced investigators to construct a meaningful study design, and the increased awareness of the disease through the SPSRF (SPS Research Foundation) which can facilitate patient recruitment.

Future Immunotherapies in SPS

Novel therapeutic approaches with monoclonal antibodies against antibody-producing B cells or plasmablasts and key cytokines that offer targeted immunotherapies similar to those in the other antibody-mediated neurologic diseases are also applicable to SPS. Although T cells may play a role as noted above and justify anticytokine therapies, the presence of antibodies in more than 80% of the patients provides more compelling reasons to focus first on antibody-targeted therapies, especially because some patients had responded to rituximab. The following agents are reasonable to pursue, as recently highlighted:

1. Anti–B-cell agents targeting CD19 and CD20, currently approved in other autoimmune neurologic diseases. These include (1) ocrelizumab given IV; (2) ofatumumab given subcutaneously; (3) inebilizumab that also targets antibody-producing CD19–positive plasmablasts and plasma cells; and (4) ublituximab, a glycoengineered anti-CD20, just approved for MS, which is also attractive because it requires low doses and short infusion durations.

2. Other anti–B-cell agents approved or in ongoing trials. These include (1) obexelimab (XmAb5871) which binds and targets not only CD19 but also the FcγRIIB, markedly enhancing the inhibitory FcγRIIB and down-regulating CD19; (2) obinutuzumab, a third generation
anti-CD20 approved for chronic lymphocytic leukemia, causing profound depletion of peripheral but also the lymphoid B cells60; and (3) bortezomib, a proteasome inhibitor used against antibody production in multiple myeloma, that also targets plasmablasts; and (4) daratumumab that targets the CD38 receptor, affecting CD20-negative long-lived plasma cells.60

3. Bruton tyrosine kinase inhibitors zanubrutinib and rilzabrutinib, which already show promise in patients with MS.61

4. FcRn inhibitors that enhance the catabolism of circulating IgG antibodies. These include efgartigimod that outcompetes endogenous IgG preventing its recycling and enhancing IgG degradation in the lysosomes, now approved for myasthenia gravis61,62; rozanolizumab, given subcutaneously with high-affinity binding to FcRn, successful in phase III trial in myasthenia gravis; batoclimab, given as a low-level weekly subcutaneous injection; and nipocalimab that ensures occupancy of FcRn throughout the IgG recycling process.62

5. Anti–interleukin-6-receptor antagonists, such as tocilizumab and also satralizumab, humanized monoclonal antibodies that bind both the soluble and the membrane-bound interleukin-6 receptor, which plays a role in B cell activation and T cell differentiation, and have been already approved for NMO-SD and show promise in N-methyl-D-aspartate receptor encephalitis.63

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Appendix
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