

HIGH-DOSE INTRAVENOUS IMMUNE GLOBULIN FOR STIFF-PERSON SYNDROME

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ABSTRACT

Background Stiff-person syndrome is a disabling central nervous system disorder with no satisfactory treatment that is characterized by muscle rigidity, episodic muscle spasms, high titers of antibodies against glutamic acid decarboxylase (GAD65), and a frequent association with autoimmune disorders. Because stiff-person syndrome is most likely immune-mediated, we evaluated the efficacy of intravenous immune globulin.

Methods We assigned 16 patients who had stiff-person syndrome and anti-GAD65 antibodies, in random order, to receive intravenous immune globulin or placebo for three months, followed by a one-month washout period and then by three months of therapy with the alternative agent. Efficacy was judged by improvements in scores on the distribution-of-stiffness index and heightened-sensitivity scale from base line (month 1) to the second and third month of each treatment phase. Direct and carryover effects of treatment were compared in the two groups.

Results Among patients who received immune globulin first, stiffness scores decreased significantly ($P=0.02$) and heightened-sensitivity scores decreased substantially during immune globulin therapy but rebounded during placebo administration. In contrast, the scores in the group that received placebo first remained constant during placebo administration but dropped significantly during immune globulin therapy ($P=0.01$). When the data were analyzed for a direct and a first-order carryover effect, there was a significant difference in stiffness scores ($P=0.01$ and $P<0.001$, respectively) between the immune globulin and placebo groups, and immune globulin therapy had a significant direct treatment effect on sensitivity scores ($P=0.03$). Eleven patients who received immune globulin became able to walk more easily or without assistance, their frequency of falls decreased, and they were able to perform work-related or household tasks. The duration of the beneficial effects of immune globulin varied from six weeks to one year. Anti-GAD65 antibody titers declined after immune globulin therapy but not after placebo administration.

Conclusions Intravenous immune globulin is a well-tolerated and effective, albeit costly, therapy for patients with stiff-person syndrome and anti-GAD65 antibodies. (N Engl J Med 2001;345:1870-6.)

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STIFF-PERSON syndrome is a rare central nervous system disorder characterized by rigidity of truncal and proximal limb muscles with intermittent superimposed spasms.¹⁻⁴ Continuous contractions of agonist and antagonist muscles caused by the involuntary firing of motor units at rest are the clinical and electrophysiologic hallmarks of the disease.⁵⁻⁷ The cause of stiff-person syndrome is unknown, but an autoimmune pathogenesis is suspected for several reasons. Circulating antibodies against glutamic acid decarboxylase (GAD65) are characteristic of the disease^{8,9} and have distinct epitope specificity.⁸⁻¹² These antibodies are produced intrathecally and may be pathogenic because they inhibit the activity and may impair the synthesis of the inhibitory neurotransmitter γ -aminobutyric acid (GABA), resulting in low levels of GABA in the brain and cerebrospinal fluid.¹³⁻¹⁶ Stiff-person syndrome is frequently found in association with other autoimmune disorders, autoantibodies, and certain HLA-DR and DQ phenotypes.^{3,4} There are anecdotal reports that treatment with prednisone, plasmapheresis, or intravenous immune globulin decreases the disabling effects of the disease.¹⁶⁻²¹

Currently, diazepam is the mainstay of therapy and helps most patients for various periods.¹⁶⁻²¹ However, the doses required are often intolerably high (up to 60 mg daily).²² As a result, most patients are left with substantial disability and need a cane or a walker owing to truncal stiffness and frequent falls.³ The need for an efficacious and safe therapy prompted the present study with intravenous immune globulin, a potent immunomodulating agent that has been effective in other autoimmune disorders.²³

METHODS

Patients

From 1996 to 1999, we enrolled 16 patients with stiff-person syndrome (9 women and 7 men) who ranged in age from 28 to 59 years (mean age, 46). All patients had had incomplete responses to therapies and fulfilled the following strictly defined clinical criteria³: rigidity of limb and axial (trunk) muscles that was prominent in the abdominal and thoracolumbar paraspinal areas and made bending difficult; clinical and electrophysiological evidence of continuous contraction of agonist and antagonist muscles¹⁶; episodic spasms precipitated by unexpected noises, tactile stimuli, or

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emotional upset; the absence of any other neurologic disease that could explain the stiffness and rigidity; and anti-GAD65 antibodies, as assessed by immunocytochemical analysis, Western blotting, and an enzyme-linked immunosorbent assay (ELISA).^{10,13} Bedridden patients and those with coronary artery disease, IgA deficiency, or kidney dysfunction were excluded.

The protocol was approved by the institutional review board of the National Institute of Neurological Disorders and Stroke. The patients gave written informed consent and were admitted to the clinical center of the National Institutes of Health. At enrollment, 16 patients were receiving benzodiazepines; 6, baclofen; 3, gabapentin; and 1, valproic acid. The doses of these drugs remained unchanged throughout the study.

Study Design

The study had a randomized, double-blind, placebo-controlled, crossover design. The placebo-controlled design was justified because of the complex and often subjective nature of the symptoms of stiff-person syndrome. The protocol specified the intravenous administration of 2 g of immune globulin per kilogram of body weight per month, divided into two consecutive daily doses of 1 g per kilogram,²⁴ or placebo, consisting of half-normal saline, once a month for three months in random order, followed by a one-month washout period and three months of treatment with the alternative agent. Immune globulin costs \$75 to \$80 per gram. Thus, for a patient who weighed 70 kg, the cost of the drug would be at least \$10,500 per month or \$31,500 for the full three-month course of treatment. Randomization was performed at the pharmacy. The bottles of intravenous immune globulin or placebo were sent to the patient's room wrapped in aluminum foil. The entire intravenous set was covered by an opaque plastic bag.²⁴ Patients were followed for at least one to two months after the infusions, with frequent contact thereafter. The randomization code was not broken until all patients had completed the study. The principal investigator, physicians, nurses, physical therapists, and statisticians were unaware of the treatment assignments. Side effects were recorded by the neurologist assigned to each patient or by the nurse coordinator. Patients were encouraged to continue their routine activities and record the frequency of falls, spasms, and any changes in their ability to carry out the activities of daily living.

Monthly Clinical Assessments

At base line and each month thereafter, the same neurologist used the distribution-of-stiffness index, the most consistent indicator of stiffness among patients and within patients,³ to evaluate the patients. Scores on this index range from 0 to 6 and reflect the extent of stiffness, with one point being given for stiffness in each of the following areas: lower trunk, upper trunk, legs, arms, face, and abdomen. Lower scores indicate less stiffness. The same neurologist also assessed the patients for changes in frequency of spasms with use of the heightened-sensitivity scale, which has been a reproducible and consistent means of assessing the number of factors triggering spasms.³ Scores range from 1 to 7, with one point being given for each source of or type of spasm, as follows: unexpected noises, visual stimuli, somatosensory stimuli, voluntary activities, emotional upset or stress, no specific stimuli, and nocturnal spasms. Lower scores indicate less frequent spasms.

Patients' Own Assessments of Response to Therapy

At the end of the study and before the code was broken, the patients were asked to guess the treatment they had received (placebo or immune globulin) during each phase of the study; to point out the phase in which their condition improved; to indicate whether the improvement was meaningful with respect to their ability to perform the activities of daily living; to specify whether their disease had remained stable, improved, or worsened; and to indicate whether, after the end of the second phase, if the improvement was clinically meaningful, they had independently attempted to receive regular immune globulin therapy on the assumption

that the improvement achieved during one phase of the study was related to immune globulin. If patients had subsequently received open-label immune globulin, they were asked to specify how long the improvement lasted after each infusion.

Measurement of Anti-GAD65 Antibody Titers

Anti-GAD65 antibody titers were measured by ELISA¹³ in coded specimens obtained before and after each three-month treatment period. Twelve patients had preinfusion and postinfusion serum samples from both phases of the study.

Statistical Analysis

The primary end point was a change in the scores of the distribution-of-stiffness index and the heightened sensitivity scale from base line (month 1) to the second and third month of each treatment. Secondary end points were changes in the patients' ability to bend at the waist, expand their chests, and perform timed activities, such as walking 9.1 m (30 ft).³ Student's *t*-test was used to assess differences in anti-GAD65 antibody titers before and at the end of each three-month treatment period.

All data were analyzed before the study code was broken, according to the linear model of Kenward and Jones.²⁵ We extended this model to accommodate eight periods of analysis and obtain unbiased estimates of any base-line differences in the two groups during each treatment phase, the direct effects of treatment on symptoms during the month after each infusion, the residual effect after three monthly infusions (first-order carryover effect), and the residual effect after the washout period (second-order carryover effect), with use of least-square techniques. Significance testing was performed by applying permutation techniques that permute the data in all possible ways and determine a *P* value for each. The net differences in the stiffness index and heightened-sensitivity scores from base line to the end of three months of treatment and the first- or second-order carryover effects were compared between the treatment groups in each period. For the distribution of stiffness, a separate subanalysis of stiffness in the trunk, abdomen, arms, legs, and face was also performed.

We also conducted a sequential analysis of the two carryover effects (at an α level of 0.05). We evaluated data for a second-order carryover effect before evaluating whether there was a first-order effect. Depending on the results of the sequential tests, the model could include both carryover effects, only the first-order effect, or neither carryover effect. For example, if the *P* value for the model that included both carryover effects was not significant, the final model would not include any carryover effects. The final model was ascertained on the basis of the two-sided *P* value for the two carryover effects and was used in the analysis of the effects of treatment and base-line differences between the two groups in each treatment period.

RESULTS

Clinical Observations at Base Line

Of the 16 patients, 8 (4 women and 4 men) were randomly assigned to receive placebo for the first three months and 8 (5 women and 3 men) were assigned to receive intravenous immune globulin first. The two groups were similar with regard to age, duration of disease, age at onset of symptoms, severity of disease, and the prevalence of other autoimmune diseases (Table 1).

Complete results could not be obtained for two patients and thus were never entered into the analysis. One man who was assigned to receive intravenous immune globulin first had a severe, long-lasting, blistering rash after each infusion that unmasked blinding. One woman who was assigned to receive placebo

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS, ACCORDING TO WHETHER THEY WERE RANDOMLY ASSIGNED TO RECEIVE IMMUNE GLOBULIN OR PLACEBO FOR THE FIRST THREE MONTHS OF THE STUDY.*

CHARACTERISTIC	IMMUNE GLOBULIN FIRST (N=8)	PLACEBO FIRST (N=8)
Age at onset (yr)		
Mean	39	41
Range	27-54	35-47
Sex (M/F)	3/5	4/4
Duration of disease (yr)		
Mean	12	11
Range	3-23	5-22
Severity of disease		
Heightened-sensitivity scores†	4.8±1.4	4.8±1.7
Distribution-of-stiffness scores‡	4.6±1.6	4.7±1.3
Coexisting autoimmune diseases (no. of patients)		
Type 1 diabetes§	3	4
Polymyositis	0	1
Pernicious anemia	0	1
Thyroiditis	3	1
Vitiligo	1	0
Seizures (no. of patients)	1	1
Medications (no. of patients)		
Benzodiazepines	7	8
Baclofen	5	2
Gabapentin	2	1
Valproic acid	1	0

*Plus-minus values are means ±SD.

†Higher scores mean more frequent spasms. The standard errors of the scores were 0.6 in the group that received placebo first and 0.5 in the group that received immune globulin first.

‡Higher scores mean more widespread stiffness. The standard errors of the scores were 0.5 in the group that received placebo first and 0.6 in the group that received immune globulin first.

§During the three-year follow-up period, diabetes developed in two additional patients who received placebo first and in one additional patient who received immune globulin first.

first had an unusual pattern of motor behavior with remarkable daily fluctuations that precluded data collection.

Efficacy

In the group that received placebo first, the mean distribution-of-stiffness scores did not change significantly during the three months of placebo administration but decreased significantly during the three months of immune globulin therapy (P=0.01) (Fig. 1A and Table 2). In contrast, the scores in the group assigned to receive immune globulin first dropped significantly (P=0.02) during the three months of immune globulin therapy, remained constant during the washout period, and then increased during placebo administration but did not return to base-line values. The differences in scores between placebo and

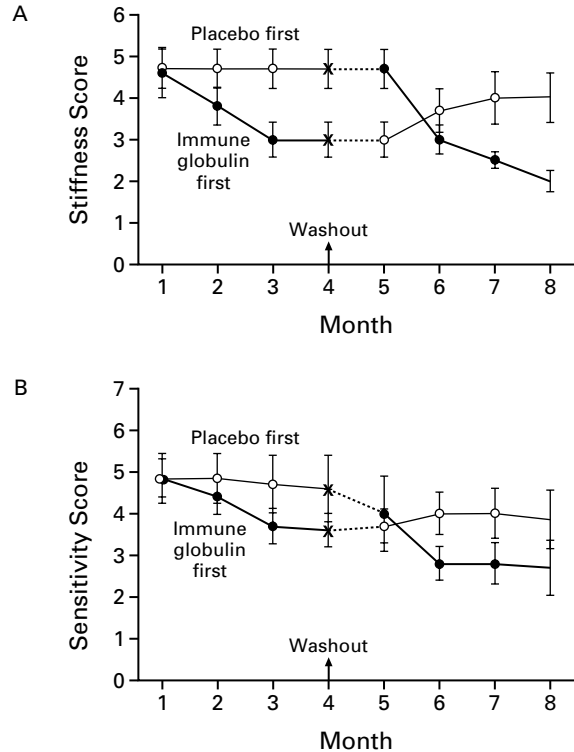


Figure 1. Mean (±SE) Distribution-of-Stiffness Scores (Panel A) and Heightened-Sensitivity Scores (Panel B), According to Whether Patients Were Assigned to Receive Immune Globulin or Placebo First.

In each scale, higher scores indicate greater impairment. Differences between placebo and immune globulin were significant at months 3, 4, 5, 7, and 8 with respect to stiffness scores (Panel A) and at months 6 and 7 with respect to heightened-sensitivity scores (Panel B). Open symbols indicate placebo administration, and solid symbols immune globulin administration.

immune globulin were significant at months 3, 4, 5, 7, and 8 (Table 2). When the overall changes were compared between the two groups, immune globulin therapy was found to have a significant direct treatment effect (P=0.01) and first-order carryover effect (P<0.001). Subanalyses showed that immune globulin therapy significantly reduced stiffness of the trunk (P<0.001 for the direct treatment effect and P=0.04 for the first-order carryover effect), abdomen (P<0.001 for the direct treatment effect), and face (P<0.001 for the first-order carryover effect).

Changes in scores on the heightened-sensitivity scale were similar to those for stiffness scores but less striking (Fig. 1B). The differences between placebo and immune globulin were not significant at any point (Table 3); however, when the data were analyzed for a direct treatment effect, the difference between the

TABLE 2. MEAN DISTRIBUTION-OF-STIFFNESS SCORES AT THE BEGINNING OF EACH MONTH OF THE STUDY, ACCORDING TO WHETHER PATIENTS WERE ASSIGNED TO RECEIVE IMMUNE GLOBULIN OR PLACEBO FIRST.*

MONTH	IMMUNE GLOBULIN FIRST	PLACEBO FIRST	P VALUE
	mean (95% CI)		
	BASE LINE	BASE LINE	
1	4.6 (3.4–5.7)	4.7 (3.7–5.7)	0.85
	IMMUNE GLOBULIN	PLACEBO	
2	3.8 (2.9–4.7)	4.7 (3.7–5.7)	0.21
3	3.0 (2.2–3.8)	4.7 (3.8–5.6)	0.02
4	3.0 (2.2–3.8)	4.7 (3.7–5.7)	0.02
	WASHOUT	WASHOUT	
5	3.0 (2.2–3.8)	4.7 (3.7–5.7)	0.02
	PLACEBO	IMMUNE GLOBULIN	
6	3.7 (2.7–4.7)	3.0 (2.3–3.7)†	0.30
7	4.0 (2.8–5.2)†	2.5 (2.1–2.9)†	0.05
8	4.0 (2.8–5.2)	2.0 (1.5–2.5)†	0.01

*Higher scores indicate more widespread stiffness. Unless otherwise indicated, data on seven patients were available at each visit. CI denotes confidence interval.

†Data on six patients were available.

immune globulin group and the placebo group was significant ($P=0.03$).

The time it took patients to walk 9.1 m decreased significantly in the group that received immune globulin first, indicating reduced stiffness and spasms ($P=0.02$ for the direct and first-order effects; $P=0.03$ for the second-order carryover effect).

Clinical Observations during the First Three Months of Treatment

Six of seven patients who received immune globulin first were able to walk more easily or without assistance for the first time in months or years (Fig. 2). The frequency of falls decreased, and their fears about crossing open spaces diminished. They were able to appear in public, socialize, cross a street without help, shower without spasms, and assume work-related or household chores. Their faces became animated. In contrast, no such objective changes occurred during the first three months in the seven patients who received placebo first.

Clinical Observations during the Second Three Months of Treatment

The condition of five of seven patients who received placebo first improved after they received immune globulin, and the condition of four of seven patients who received immune globulin first wor-

TABLE 3. MEAN HEIGHTENED-SENSITIVITY SCORES AT THE BEGINNING OF EACH MONTH OF THE STUDY, ACCORDING TO WHETHER PATIENTS WERE ASSIGNED TO RECEIVE IMMUNE GLOBULIN OR PLACEBO FIRST.*

MONTH	IMMUNE GLOBULIN FIRST	PLACEBO FIRST	P VALUE
	mean (95% CI)		
	BASE LINE	BASE LINE	
1	4.8 (3.9–5.7)	4.8 (3.7–6.0)	1.00
	IMMUNE GLOBULIN	PLACEBO	
2	4.4 (3.6–5.2)	4.9 (3.7–6.0)	0.56
3	3.7 (2.9–4.5)	4.7 (3.3–6.0)	0.23
4	3.6 (2.9–4.3)	4.6 (3.1–6.1)	0.27
	WASHOUT	WASHOUT	
5	3.7 (2.9–4.5)	4.0 (2.2–5.8)†	0.77
	PLACEBO	IMMUNE GLOBULIN	
6	4.0 (3.0–5.0)	2.8 (2.0–3.6)†	0.09
7	4.0 (2.8–5.2)†	2.8 (1.9–3.7)†	0.15
8	3.8 (1.4–5.2)	2.6 (1.3–4.0)†	0.25

*Higher scores indicate more frequent spasms. Unless otherwise indicated, data on seven patients were available at each visit. CI denotes confidence interval.

†Data on six patients were available.

sened once they began to receive placebo. The condition of one patient who received placebo first worsened substantially during the three months of placebo treatment and was marked by continuous spasms and stiffness (status spasticus)³ by the time the crossover phase began. The life-threatening nature of this state prompted us to break the code. The patient's condition improved dramatically after he crossed over to immune globulin. Overall, 11 patients had clinical improvement after receiving immune globulin, according to observations made before the study code was broken.

Patients' Own Assessments and Follow-up

Of 14 patients who were contacted after the results were analyzed (the spouses of 2 patients who died were contacted), 12 readily identified the treatment phase on the basis of the unequivocal improvement in their condition during that time. One patient, who received immune globulin first, had a slight improvement that was maintained throughout the study, presumably owing to a sustained carryover effect, and could not distinguish one phase from the other. This patient did not wish to pursue further treatment with immune globulin. The other patient, who received placebo first, recalled having a gradual improvement throughout the study.

Two patients died after the study: one from gas-



Figure 2. A Representative Patient with Stiff-Person Syndrome before (Panel A) and after (Panel B) Treatment with Immune Globulin. Before treatment, the patient required a walker (Panel A). Her gait was slow and deliberate, and she had noticeable stiffness of her back and legs. After completing treatment with intravenous immune globulin, she was able to walk unaided and to bend forward (Panel B). She was more mobile and less stiff. She had fewer anxiety-triggered spasms, and she was able to resume household chores.

traintestinal bleeding a year after the study and the other from cardiac arrest two years after the study. Both had sought and received immune globulin therapy after the study. Of the other patients who successfully pursued continued immune globulin treatment, seven require infusions every 5 to 12 weeks and one other requires them every 4 months in order to engage in routine daily activities. Two patients did not need any additional treatment for up to a year. One patient was unable to obtain approval for immune globulin therapy from the insurance company.

Anti-GAD65 Antibody Titers

Anti-GAD65 antibody titers were measured in six patients in each group. Anti-GAD65 antibody titers remained stable in patients who received placebo first, whereas they decreased by 33 percent in patients who received immune globulin first and then rebounded significantly ($P=0.03$) during placebo ad-

ministration (Fig. 3). Although after the first three months, the difference in antibody titers was not significant between the two groups (Fig. 3), the titers were found to have declined significantly ($P=0.05$) after immune globulin therapy when the data for the second period were also included and compared (data not shown). Weekly determinations of antibodies in two patients showed that titers began to fall by the seventh day after the infusion and reached a nadir within three weeks (data not shown). The anti-GAD65 antibody titers did not correlate with the severity of disease, and the reduction in titers was not correlated with the degree of improvement in the patients' clinical condition.

DISCUSSION

Our findings demonstrate that, as used, intravenous immune globulin is a safe and effective therapy for stiff-person syndrome. This conclusion is based

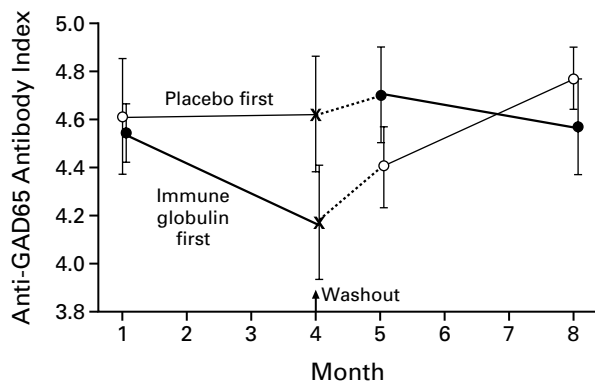


Figure 3. Mean (\pm SE) Anti-Glutamic Acid Decarboxylase (GAD65) Antibody Titers before and after Each Three-Month Treatment Period in Six Patients Assigned to Receive Immune Globulin First and Six Patients Assigned to Receive Placebo First. Titers are expressed in terms of a logarithmic antibody index. In the group that received immune globulin first, the mean titers decreased by 33 percent after three months of immune globulin and then increased significantly ($P=0.03$) after three months of placebo. Open symbols indicate placebo administration, and solid symbols immune globulin administration.

on the objective improvement after the administration of immune globulin, as compared with placebo, and is supported by the increased ability of the patients to perform the activities of daily living.

Up to 65 percent of patients with stiff-person syndrome cannot perform routine daily activities because of total-body stiffness, fear of falling, anxiety-triggered spasms, and frequent falls.³ Others use walkers or wheelchairs, and still others are bedridden because of severe stiffness. Our results show an improvement in the symptoms of most patients who completed the study, according to objective data obtained through reproducible instruments that measure stiffness and sensitivity to stimuli that trigger spasms. Immune globulin therapy had a positive effect on the degree of stiffness; the frequency of falls; the ability to walk unaided, shower independently without spasms, and work or perform household chores; and the number of episodic spasms triggered by unexpected noises, tactile stimuli, fear, or emotional upset.

The role of anti-GAD65 antibodies in the autoimmune pathogenesis of stiff-person syndrome has been questioned because GAD65 is a cytoplasmic antigen and the few autopsy studies that have been performed did not find substantial histologic changes in the brains of affected patients.¹¹ However, studies found that anti-GAD65-specific IgG from patients with stiff-person syndrome (but not from controls) inhibited GAD65 activity in vitro and impaired the synthesis of GABA without causing identifiable structural changes in GABAergic neurons.^{14,15} Furthermore,

anti-GAD65 antibodies are produced intrathecally and suppress GABA levels in the brain and cerebrospinal fluid of affected patients.^{13,16} The predominant inhibitory neurotransmitter in the brain is GABA, accounting for 25 to 35 percent of all synapses; thus, a reduction in GABA due to anti-GAD65 antibodies could easily explain the muscle hyperactivity of stiff-person syndrome. Our finding that intravenous immune globulin decreased the symptoms of the disease supports the view that stiff-person syndrome is a functional rather than structural disorder, with an ongoing immune response that impairs GABAergic transmission without causing structural changes in the brain. Because GABA is involved in many brain circuits that control muscle tone, autonomic responses, fear, arousal, and behavior,²⁶ increased transmission of GABA as a result of the immunoregulatory effects of immune globulin can explain the reduction in both muscle stiffness and the frequency of spasms triggered by fear and emotional upsets in our patients.

Although the anti-GAD65 antibodies declined after immune globulin therapy was stopped, the titers did not correlate with either the severity of disease or the magnitude of the clinical response. If anti-GAD65 antibodies are pathogenic in stiff-person syndrome, immune globulin may have inhibited their activity by accelerating the rate of IgG catabolism,²⁷ by acting directly on Fc receptors of B cells to suppress autoantibody production, or by inducing anti-idiotypic antibodies.²⁸ The concept of a delayed action of anti-idiotypic antibodies is supported by our preliminary findings that anti-GAD65 antibody titers declined within a week after the administration of immune globulin and reached a nadir within three weeks. The other immunomodulatory effects of immune globulin on T cells and cytokines²³ may also have had a complementary role in suppressing disease activity.

In some of the patients, the efficacy of immune globulin was short-lived (lasting up to six weeks) — a response that is commonly seen in other autoimmune neuromuscular disorders.²³ In some patients, however, the benefit was sustained, lasting up to a year. The mechanisms of such a long-lasting effect are unclear. If untreated, stiff-person syndrome can result in total disability^{3,29} and is rarely controlled by diazepam or other available agents. Our findings indicate that, as used, intravenous immune globulin is safe, well tolerated, and effective, although very expensive, for stiff-person syndrome and significantly improves patients' ability to perform the activities of daily living and, thus, their quality of life.

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