Lack of Effect of Intravenous Immunoglobulins on Tics: A Double-Blind Placebo-Controlled Study

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Background: Case studies and a placebo-controlled study previously suggested the effectiveness of immunomodulatory therapy in patients with tic or related disorders whose symptoms show a relationship with streptococcal infections. No data are available on the effectiveness of intravenous immunoglobulins (IVIG) on tic severity in unselected tic disorder patients.

Method: Thirty patients with a DSM-IV tic disorder were randomly assigned to IVIG (1 g/kg on 2 consecutive days; mean age = 28.71 years; range, 14–53 years) or placebo (mean age = 30.73 years; range, 14–63 years). Symptoms were rated with the Yale Global Tic Severity Scale, the Yale-Brown Obsessive Compulsive Scale, and the Clinical Global Impressions scale of symptom change with regard to tic severity. These were used at baseline and on weeks 2, 4, 6, 10, and 14 posttreatment, after which blinding was broken. The study was conducted from March through August 2002.

Results: We observed no significant differences between both treatment groups regarding posttreatment changes in tic severity. Severity of obsessions and compulsions, which was in the subclinical range, decreased significantly in the IVIG group compared with the placebo group at week 6 ($p = .02$). Then, there was a 32.3% improvement in the IVIG group compared with baseline. Though this improvement was maintained over the following 8 weeks, no statistically significant differences between the IVIG and the placebo group with regard to improvements in obsessions and compulsions were detected at subsequent assessments. IVIG treatment was associated with significantly more side effects than placebo, most notably headache.

Conclusion: Based on the present results, IVIG cannot be recommended in tic disorders.

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Tic disorders, formerly thought to have a psychogenic cause,[1] are now generally regarded as neurobiological disorders with a strong genetic component.[2] These disorders are characterized by the presence of recurrent sudden movements and/or utterances, frequently accompanied by associated behavioral difficulties such as hyperactivity/impulsivity, attentional problems, emotional lability, rage attacks, and obsessive-compulsive symptoms.[3] Though symptoms may improve after the onset of puberty,[4] a considerable number of patients suffer their whole lives from this debilitating symptomatology.

Intriguing recent research findings support the possible involvement of autoimmunity in tic disorders.[5] Infections are thought to induce symptom exacerbations,[6] possibly through the involvement of antineuronal autoantibodies.[7] The relationship between infections and symptom fluctuations is most evident in cases fulfilling criteria for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS),[8] but may also apply to a broader range of tic disorder patients, as recently discussed.[5]

The relevance of immunologic factors may have important treatment implications. Indeed, some published case studies reported the successful application of immunomodulatory therapies in patients with tic disorders, mostly reported in cases fulfilling PANDAS criteria. These included immunosuppression with corticosteroids,[9–11] therapeutic plasma exchange,[12,13] and intravenously administered immunoglobulins (IVIG).[13–15]

Only a single placebo-controlled study is available with regard to immunologic treatments.[16] That study pointed to the effectiveness of both plasma exchange and IVIG in pediatric tic and obsessive-compulsive disorder (OCD) patients who all met PANDAS criteria,[8] compared with a placebo condition. Interestingly, a single course of plasma exchange or IVIG resulted in positive effects that were still present at 1 year after treatment. Treatment with IVIG resulted in significant improvements in obsessive-compulsive symptoms, anxiety, and depression. However, the IVIG group did not show significant improvement in tic severity.

Since the study by Perlmutter et al.[16] included 2 different disorders—OCD and/or tic disorders—the number of patients with tics in that study was rather low (8 children

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with tics in the placebo group vs. 4 in the IVIG group). In addition, given the PANDAS criteria that subjects had to meet, which require evidence of an association between streptococcal infection and onset or exacerbation of signs and symptoms, the patients who were enrolled in the study may well not be representative of tic disorder patients in general. In other words, whether IVIG benefits tic severity in unselected patients with a tic disorder has not been addressed. This is an important issue, given the possible involvement of immune factors across tic disorder patients who were not specifically preselected using PANDAS.[6,17]

Meanwhile, the imposing results of the single placebo-controlled study[16] as well as the published highly successful case reports[13–15] (information that is readily accessible to a lay public via the Internet) have occasionally led to considerable pressure inflicted on clinicians by tic disorder patients or their parents to apply one of the immunomodulatory treatment options. Also, many clinicians themselves wonder if they should refer their patients with tic or related disorders to such treatment modalities, especially given the paucity of currently available treatment possibilities, which consist largely of the use of antipsychotic agents that may have troublesome side effects. This situation led us to conduct the present double-blind study in which we compared the therapeutic effect of a single course of IVIG with a placebo condition in a group of unselected patients with a chronic tic disorder. We used changes in tic severity as the primary endpoint of the study. In addition, we assessed changes in obsessive-compulsive symptoms. Contrary to the study by Perlmutter et al.,[16] who studied children aged 5 to 14 years, we decided to enroll patients aged 14 years and older, including adult patients. Spontaneous, long-lasting remissions in tic severity are far less likely to occur in older patients, especially adults, than in prepubertal children.[18] Thus, development of effective treatment options is most urgently needed for those older patients, who continue to show bothersome tics. We hypothesized that IVIG treatment would be more effective than placebo in lessening severity of tics and obsessive-compulsive symptoms.

METHOD

Patient Recruitment

Patients aged 14 years or older with a DSM-IV tic disorder were recruited from 2 sources: from members of the Tourette's syndrome patient's association in the Netherlands and from patients who had been referred to the outpatient clinic of the Child and Adolescent Psychiatry Center in Groningen, the Netherlands. Patients of both groups received a written invitation to participate in the study. This letter provided information about the aims and background of the study. A total of 64 patients (21 from our outpatient clinic and 43 from the patient's association) were initially interested in participating and were assessed for study eligibility by the first author (P.J.H.).

Eligibility criteria included fulfillment of the research criteria for a definite tic disorder according to the Tourette Syndrome Classification Study Group[19] (implying that observable tics have to be present during the clinical interview to allow for study entry) and presence of tics severe enough to cause significant distress and interference with the patient's functioning in at least 2 spheres (home, school, work, social relationships). This tic severity requirement was based on the subjective experience of patients and not on a formal tic rating cut-off. In addition, the presence of a tic disorder had to be the primary problem. Though none of the patients met PANDAS criteria,[8] these were not used as an exclusion criterion. Excluded from the study were subjects with total IgA deficiency and anti-IgA antibodies, given the risk of anaphylactic reactions caused by IgE class anti-IgA antibodies reacting with IgA in the IVIG preparation. Therefore, all patients were screened with regard to IgA deficiency. This was detected in none of the subjects who were willing to participate.

The aim and procedure of the study were fully explained to the subjects before written consent was requested. If the subjects were under 18, the written informed consent of the parents was obtained along with that of the subject. The study was approved by the Dutch central medical-ethical committee (The Hague, the Netherlands), and was in accordance with the Helsinki Declaration of 1975, as revised in 1983. Thirty-four patients did not meet inclusion criteria or were unwilling to give final consent; the remaining 30 patients (8 from our outpatient clinic and 22 from the patient's association) were subjected to randomization. All patients from the patient's association had in the past been referred to a mental health service. Thus, all participating patients can be regarded as referred patients.

Treatment

The 30 tic disorder patients were en bloc randomly assigned to IVIG or placebo, with stratification by sex and age (above and below 18 years). Treatment of all patients was subsequently scheduled within a period of 14 weeks onward. Patients assigned to IVIG treatment received 1 g/kg of immunoglobulins (Gammagard, Baxter, the Netherlands) daily for 2 consecutive days. Gammagard is a sterile, freeze-dried preparation of at least 90% IgG, purified from large pools of human plasma from at least 1000 donors. The placebo infusion consisted of an equal volume of 5% albumin solution in the same vehicle prepared by the manufacturer of the immunoglobulins, which was also administered daily for 2 consecutive days. Investigators, nurses, and patients were unaware of the treatment assignments.

All treatments took place at the day care facility of the University Hospital Groningen, Groningen, the Nether-

lands. After an initial dose of 0.5 mg/kg/min over a period of 30 minutes, the infusions were administered at a rate of 3 mg/kg/min over a period of 5 to 6 hours. Vital signs, including blood pressure, were monitored throughout the infusion.

The first investigator (P.J.H.), who performed all pretreatment and posttreatment psychiatric assessments, was kept unaware of the occurrence of side effects, which might have revealed the active treatment. Patients were explicitly asked not to discuss these with the first investigator at all assessments. Mild side effects were to be treated symptomatically. Acetaminophen was to be used in the case of headache, flu-like symptoms, and fever, whereas mild adverse reactions (simple urticaria) were to be treated symptomatically with antihistamines. Treatment-resistant headache, flu-like symptoms, or fever would lead to a maximum 24-hour interruption of study medication. Repeated adverse events would cause discontinuation of treatment. Side effects were recorded by each patient on a form listing possible IVIG-associated side effects.

Throughout the trial, patients were free to continue or adjust any neuropsychiatric medication, as appropriate according to their physicians, with no limits on the permissible dose adjustment. This was done for ethical reasons, given the unproven effectiveness of IVIG.

Evaluation

Changes in tic severity as assessed by the Yale Global Tic Severity Scale (YGTSS)[20] were the primary endpoint of the study. This scale provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic symptoms, based on direct examination and historical data from multiple informants. In addition, we assessed posttreatment changes in severity of obsessions and compulsions.

Standardized ratings of neuropsychiatric signs and symptoms were obtained for each patient at baseline. These consisted of the YGTSS (of which we used only the sum of the motor and vocal tic score), the Yale-Brown Obsessive Compulsive Scale (YBOCS)[21,22] or the children's version[23] for subjects below 16 years of age, and the Clinical Global Impressions (CGI) scale of symptom change with regard to tic severity.[24] For the statistical analyses with the latter scale, we decided to combine the categories "very much improved" and "much improved" into the category "treatment response," and to combine all other categories ("minimally improved," "no change," "minimally worse," "much worse," and "very much worse") into 1 category, "no treatment response."

Evaluations of severity of neuropsychiatric signs and symptoms were scheduled at weeks 2, 4, 6, 10, and 14 after treatment. Serum creatinine was measured at baseline and on day 3. After the final evaluation of the last patient, the IVIG/placebo masking was broken en bloc. Results were analyzed on the basis of intention to treat. Patients were not asked which treatment they thought they had received. The whole study, including blinded follow-up, was conducted from March through August 2002.

Table 1. Baseline Characteristics of Tic Disorder Patients

Characteristic	IVIG (N = 14)	Placebo (N = 15)
Age, mean (range), y	28.71 (14–53)	30.73 (14–63)
Gender, N (%)		
Men	9 (64.3)	9 (60.0)
Women	5 (35.7)	6 (40.0)
Medication status, N (%)		
None	6 (42.9)	7 (46.7)
Neuroleptic	3 (21.4)	7 (46.7)
Neuroleptic + AO	2 (14.3)	0 (0.0)
AO	3 (21.4)	1 (6.7)
Symptom severity score, mean (SD)		
YGTSS[a]	25.0 (9.6)	25.5 (8.9)
YBOCS[b]	10.2 (9.2)	5.6 (7.8)
Type of tic disorder, N (%)		
TD	13 (92.9)	13 (86.7)
CMT	1 (7.1)	2 (13.3)

[a]Sum of motor and vocal scores.
[b]YBOCS or children's version for subjects below 16 years of age.
Abbreviations: AO = antiobsessional agent, CMT = chronic motor tic disorder, IVIG = intravenous immunoglobulins, TD = Tourette's disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale, YGTSS = Yale Global Tic Severity Scale.

Statistical Analysis

To measure differences between groups at baseline and subsequent assessments after treatment, we used repeated-measures analysis of variance (ANOVA) on each of the neuropsychiatric ratings by use of the SPSS statistical program, version 10.0.5 (Chicago, Ill.). Differences in outcome on the CGI scale of symptom change between both treatment groups were tested by chi-square analysis. Chi-square analysis was also used to test for differences in the occurrence of side effects. Differences in baseline severity between both treatment groups were assessed by the Mann-Whitney U test. All tests of significance used the .05 level of significance and were 2-tailed.

RESULTS

Patient Characteristics

One scheduled patient chose to withdraw from the trial before treatment. This subject had been randomly assigned to receive IVIG. Thus, 14 patients received IVIG and 15 patients received placebo. Patient characteristics of the 2 randomized groups are shown in Table 1. Both groups were comparable in age, sex, tic disorder diagnosis (DSM-IV), and use of psychotropic medication. At baseline, tic severity and severity of obsessions and compulsions did not differ significantly. None of the patients fully met DSM-IV criteria for OCD; severity of obsessions and compulsions was in the subclinical range. No patients were lost on follow-up.

Table 2. Mean Symptom Severity at Baseline and at Different Posttreatment Points, Compared With Baseline, as Well as Percentages of Treatment Responders[a]

	Baseline		Week 2			Week 4			Week 6			Week 10			Week 14		
Rating Scale	IVIG	Placebo	IVIG	Placebo	p	IVIG	Placebo	p	IVIG	Placebo	p	IVIG	Placebo	p	IVIG	Placebo	p
YGTSS score[b]	25.0	25.5	22.9	22.5	.77	24.4	21.3	.17	21.1	22.4	.77	22.1	24.3	.40	20.1	24.3	.18
YBOCS score[c]	10.2	5.6	6.1	4.5	.11	9.2	3.7	.50	6.9	5.4	.02	6.4	4.6	.13	6.7	4.5	.11
% responders			7.1	33.3	.08	7.1	33.3	.08	14.3	26.7	.41	21.4	13.3	.56	28.6	6.7	.12

[a]Treatment response was based on the presence or absence of a "very much" or "much improvement" rating according to the Clinical Global Impressions scale of symptom change, with regard to tic severity. The p values represent significance levels of repeated-measures ANOVA with regard to differences in treatment response between patients who received IVIG treatment and patients who received placebo, and significance levels of chi-square analyses regarding differences in percentages of treatment responders between treatment groups, respectively.
[b]Sum of motor and vocal scores (range, 0–50).
[c]YBOCS or children's version for subjects below 16 years of age (range, 0–40).
Abbreviations: ANOVA = analysis of variance, IVIG = intravenous immunoglobulins, YBOCS = Yale-Brown Obsessive Compulsive Scale, YGTSS = Yale Global Tic Severity Scale.

Table 3. Occurrence of Mild-to-Moderate Side Effects in Both Treatment Groups

	IVIG (N = 14)		Placebo (N = 15)		
Side Effect	N	%	N	%	p*
Any side effect	13	93	4	27	< .001
Chills	6	43	1	7	.023
Headache	11	79	4	27	.005
Fever	5	36	0	0	.011
Vomiting	4	29	0	0	.026
Nausea	7	50	1	7	.009
Dizziness	3	21	0	0	.058

*p Values represent significance levels for differences between groups (Pearson chi-square).
Abbreviation: IVIG = intravenous immunoglobulins.

Treatment Response

No significant differences were observed between both treatment groups with regard to posttreatment changes in tic severity (Table 2). In both the IVIG group and the placebo group, posttreatment ratings of tic severity were slightly lower compared with baseline, between 2.4% and 19.6% for the IVIG group and 4.7% and 16.5% for the placebo group, depending on the posttreatment week. Regarding changes in severity of obsessions and compulsions, a significant difference between both treatment groups was observed only at week 6 (repeated measures ANOVA; $F = 5.7$, $p = .02$). At that time point, there was a 32.3% improvement in the IVIG group compared with the baseline level. In contrast, improvement in the placebo group was 3.6% compared with baseline at week 6. Though improvement in obsessions and compulsions was maintained over the following 8 weeks (Table 2), no statistically significant differences between the IVIG and the placebo group with regard to improvements in obsessions and compulsions were detected at subsequent assessments.

Treatment response, as determined by the CGI scale of symptom change, ranged between 6.7% and 33.3% in both treatment groups at the different posttreatment time points. Chi-square analysis did not reveal differences in number of responders between treatment groups (Table 2). Four patients recorded changes in the use of psychotropic medication during the trial. Two patients stopped their haloperidol medication, which they both had used in a dose of 1 mg once daily. One other patient started to use haloperidol, also in a dose of 1 mg daily. The final patient who recorded medication changes had lowered his risperidone medication by 1 mg, while at the same time increasing his haloperidol dose by 1 mg. All patients who changed their medication fell in the placebo group. The changes in psychotropic medication did not lead to the category "treatment response" in all 4 cases, however.

Side Effects of Treatment

Mild-to-moderate side effects were reported by 4 patients (27%) receiving placebo versus 13 (93%) of 14 patients receiving IVIG. Table 3 shows the most frequently observed side effects. Most side effects tended to occur during the second day of the infusion. The use of acetaminophen was greater in the IVIG group than in the placebo group (71% vs. 27%; Pearson $\chi^2 = 5.8$, $p = .016$). Antihistamines for treating adverse reactions were used in 3 patients (21%), all belonging to the IVIG group. Severe treatment-resistant headache led to a 24-hour interruption of medication on the second day in 1 patient, which implied that the rest of the dose was given on the third day. This patient belonged to the IVIG group.

Due to treatment-resistant difficulty in breathing, 1 patient, who belonged to the IVIG group, discontinued treatment on the second day of the infusion. This patient had received 1 g/kg IVIG on the first day, as scheduled, and had finished 12.5% of the planned amount of IVIG on the second day. The first investigator, who performed all pretreatment and posttreatment psychiatric assessments, never became aware of the occurrence of adverse events before deblinding.

DISCUSSION

This is the first double-blind placebo-controlled study in which the effect of IVIG is examined in unselected chronic tic disorder patients, either Tourette's disorder or

chronic motor tic disorder, 2 etiologically closely related disorders.[25] According to our data, IVIG does not appear to be an effective treatment with regard to reducing tic severity in these patients.

One major difference from the earlier study by Perlmutter et al.[16] is our use of a patient group whose main feature was the presence of tics, while the study by Perlmutter et al.[16] involved children who did or did not have tics and whose primary problems were in the field of obsessions, compulsions, and emotional problems, including anxiety and depressive symptoms. A second major difference is that our patients did not meet PANDAS criteria, contrary to the study by Perlmutter et al.[16] Finally, the present study involved adolescent and adult patients as opposed to the pediatric patients in the study by Perlmutter and colleagues.[16] Still, regarding effect on tic severity, our results are in accordance with the latter study,[16] which also did not show improvement in tic severity after IVIG.

Apart from the possibility that IVIG may have no effect on tics, a number of other factors may explain the lack of treatment response in the present study. First, patients in our study had experienced many years of disease, which may be associated with nonreversible damage to relevant neuronal circuits. Moreover, the patients had access to psychotropic medication both prior to and during the trial, and thus form a treated patient population. This makes it more difficult to detect a positive effect from a new treatment, which increases the risk of a type II error. Another risk for a type II error may be the relatively low number of patients in each treatment arm. Furthermore, patients were not preselected with regard to a presumed autoimmune etiology, based on either clinical criteria[8] or laboratory parameters.[26] The present study cannot rule out that highly selected patients may still profit from treatment with IVIG. Finally, we used only a single IVIG dose, as did Perlmutter and coworkers,[16] whereas many IVIG treatment protocols use repeated, often monthly IVIG applications over time.[27] It may still be that multiple IVIG doses over a longer period of time appear to demonstrate efficacy in lessening of tic severity. However, the present available data from both our and Perlmutter's study[16] do not lend support to the application of IVIG in tic disorder patients.

Although we studied patients with a primary diagnosis of a tic disorder, we did find a significant effect regarding improvement of obsessive-compulsive symptoms in the IVIG group. At week 6 posttreatment, ratings of obsessions and compulsions had been decreased by 32% in the IVIG group. While this improvement was maintained over the following 8 weeks, differences between the IVIG and the placebo group with regard to improvements in obsessions and compulsions did not reach statistical significance at subsequent assessments.

Also in the study by Perlmutter et al.,[16] IVIG appeared to benefit severity of obsessions and compulsions. Thus, there is some indication that IVIG may improve obsessions and compulsions. Still, the present results regarding possible effectiveness of IVIG for symptoms of OCD should be viewed with much caution, given the fact that obsessions and compulsions were by no means the patients' main symptoms. In fact, baseline ratings for OCD symptoms were rather low in our study, and were in the subclinical range. Thus, observed improvements should not be considered clinically significant. In addition, the between-group difference in improvement of OCD symptoms at week 6 posttreatment may have been related primarily to a floor effect, due to the very low YBOCS baseline rating in the placebo group. Future studies should specifically study the effect of IVIG in patients with different subtypes of OCD, e.g., pediatric onset versus adult onset OCD, OCD with tics versus OCD without tics, and OCD with and without poststreptococcal exacerbations.

Contrary to Perlmutter et al.,[16] we found a relatively high placebo response in our study, with 33% of patients in the placebo group being much or very much improved at 2 weeks posttreatment. While we do not have an explanation for the striking lack of placebo effect in the study by Perlmutter et al.,[16] the sizeable placebo response that we encountered may well explain some of the successes of the case studies that reported improvement after immune-based therapy,[13–15] as well as some of the effect of the plasma exchange in the study by Perlmutter et al.,[16] which was not placebo-controlled. Thus, future studies should use blinded and well-controlled designs.

In conclusion, based on the present results, we cannot recommend IVIG treatment for reducing tic severity. Moreover, at present, the use of IVIG in OCD patients should be confined to placebo-controlled research protocols.

Drug names: acetaminophen (Tylenol and others), haloperidol (Haldol and others), intravenous immunoglobulins (Gammagard), risperidone (Risperdal).

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