

Intravenous Immunoglobulin Treatment Following the First Demyelinating Event Suggestive of Multiple Sclerosis

A Randomized, Double-blind, Placebo-Controlled Trial

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Background: Intravenous immunoglobulin (IVIg) has been reported to reduce disease activity in patients with relapsing-remitting multiple sclerosis. We assessed the effect of IVIg treatment in patients after the first neurological event suggestive of demyelinating disease and evaluated the occurrence of a second attack and dissemination in time demonstrated by brain magnetic resonance imaging within the first year from onset.

Methods: We conducted a randomized, placebo-controlled, double-blind study in 91 eligible patients enrolled within the first 6 weeks of neurological symptoms. Patients were randomly assigned to receive IVIg treatment (2-g/kg loading dose) or placebo, with boosters (0.4 g/kg) given once every 6 weeks for 1 year. Neurological and clinical assessments were done every 3 months, and brain magnetic resonance imaging was performed at baseline and the end of the study.

Results: The cumulative probability of developing clinically

definite multiple sclerosis was significantly lower in the IVIg treatment group compared with the placebo group (rate ratio, 0.36 [95% confidence interval, 0.15-0.88]; $P=.03$). Patients in the IVIg treatment group had a significant reduction in the volume and number of T2-weighted lesions and in the volume of gadolinium-enhancing lesions as compared with the placebo group ($P=.01$, $P=.01$, and $P=.03$, respectively). Treatment was well tolerated, compliance was high, and incidence of adverse effects did not differ significantly between groups.

Conclusions: Intravenous immunoglobulin treatment for the first year from onset of the first neurological event suggestive of demyelinating disease significantly lowers the incidence of a second attack and reduces disease activity as measured by brain magnetic resonance imaging.

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MULTIPLE SCLEROSIS (MS) is a chronic inflammatory demyelinating disease affecting the brain and spinal cord, in which infiltrating lymphocytes, predominantly T cells, and macrophages lead to damage of the myelin sheath.¹ Disease onset is characterized by impairment in 1 or more of the following pathways: motor, sensory, cerebellar, visual,

brainstem, or cognitive, as well as symptoms of fatigue and urinary tract dysfunction, all compatible with central nervous system involvement. During this early

stage, patients are diagnosed with the first neurological event suggestive of MS because the diagnosis of clinically definite MS requires the occurrence of a second neurological event or dissemination in time demonstrated by brain magnetic resonance imaging (MRI).²⁻⁴ The evolution of the disease has been shown to be affected by the time to occurrence of the second attack, as well as by the number of attacks within the first year.^{5,6} Prospective follow-up studies demonstrate that the proportion of patients who will progress to definite MS within the first year following the initial event is as high as 56.7%.⁷ Moreover, estimates of cognitive impairment among patients diagnosed with probable MS showed that 57% are affected within 1 month from onset.⁸ These findings, taken together with previous stud-

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ies^{9,10} demonstrating axonal loss early in the course of the disease, support the rationale for early treatment following the first demyelinating event suggestive of MS.

With the advent of immunomodulating drugs, 2 large studies (ETOMS¹¹ and CHAMPS¹²) were designed to assess the efficacy of interferon- β treatment initiated after the first demyelinating event. Both studies demonstrated a significant beneficial effect of early treatment on disease course.

Intravenously administered immunoglobulin (IVIg) treatment has been reported to be beneficial in the treatment of patients with relapsing-remitting MS.¹³ Relapse rate, relapse severity, progression of disability, and disease activity evaluated by brain MRI were all found to be positively affected by IVIg treatment. This treatment has several advantages; it can be administered during pregnancy and lactation, safety is established, and the favorable adverse effects profile leads to good compliance.¹⁴

The present randomized, double-blind, placebo-controlled trial was designed to evaluate the effects of IVIg treatment on the rate of occurrence of the second attack as well as dissemination in time demonstrated by brain MRI during the first year from onset of neurological symptoms.

METHODS

SUBJECTS

The study was conducted at the Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, Israel, from March 1998 until March 2003. The study protocol and informed consent forms were approved by the institutional review board, and all patients gave written informed consent for participation. Eligible subjects were aged between 15 and 50 years, with the first well-defined neurological event consistent with demyelination and confirmed by neurological examination and brain MRI. These patients were defined as having the first demyelinating event suggestive of MS (clinical probable MS C2 or clinical probable MS C3, according to Poser criteria,² or possible MS according to McDonald criteria³). The onset of the neurological symptoms was limited to 90 days prior to randomization. Partial or complete regression of the neurological symptoms to exclude a primary progressive course was a requisite for participation. Patients also had to have abnormal brain MRI results according to Fazekas criteria.⁴ Patients were excluded if they had IgA deficiency, a positive pregnancy test, sensitivity to gadolinium contrast material or sensitivity to human blood products.

TREATMENT ASSIGNMENT AND MONITORING

The study was a priori designed as a randomized, double-blind, placebo-controlled trial. Patients' allocation was based on a block-stratified randomization procedure, and accordingly, they were randomly assigned to each of the 2 treatment groups. One group of patients received 0.4 g/kg body weight per day of IVIg (Omr-IgG-am, Omrix Biopharmaceuticals Ltd, Ramat-Gann, Israel) for 5 consecutive days (loading dose) followed by 0.4 g/kg body weight per day of IVIg once every 6 weeks for a period of 1 year. The other group received placebo in the form of intravenously administered 0.9% sodium chloride in identical settings and regime.

At the pharmacy, containers and tubing of IVIg or saline were wrapped in sealed opaque bags. At baseline and once every 3 months, blood was obtained for hematologic and serum chemistry analysis.

STUDY PROCEDURES AND END POINTS

Each patient was evaluated by an examining neurologist who was unaware of the patient's treatment assignment. Subsequent examinations were scheduled once every 3 months. In each examination, a complete neurological status was performed and disability was scored in accordance with the Expanded Disability Status Scale (EDSS).¹⁵ During a suspected relapse, a patient was examined twice in the same visit. The changes on neurological examination to determine whether a relapse had occurred were based on the neurological examination performed by 2 evaluating neurologists both unaware of treatment assignment. On confirmation of a relapse by any 1 of the 2 neurologists, the patient was withdrawn from the study. Relapse was defined as the onset of new neurological symptoms suggestive of white matter involvement, occurring for a period of at least 48 hours and accompanied by objective neurological findings assessed by the EDSS.

The primary end point was defined as the number of patients who experienced a second attack thereby fulfilling the criteria for the diagnosis of MS within 1 year. Secondary outcome measures were the change in MRI disease burden, neurological disability (EDSS), and cognitive performance.

MRI LESION LOAD

Brain MRI was performed at baseline and at study completion or discontinuation. Examinations were obtained using a 2.0-T imager (Elscent, Haifa, Israel). For each MRI examination, the following data were acquired: (1) sagittal T1-weighted localizer images (repetition time, 500 milliseconds; echo time, 12 milliseconds), 24-cm field of view, 256 \times 180 matrix; (2) axial dual spin-echo (proton density and T2) weighted sequences (repetition time, 5500 milliseconds; echo time, 16-128 milliseconds), 22-cm field of view, 256 \times 256 matrix; (3) axial T1-weighted images (repetition time, 500 milliseconds; echo time, 12 milliseconds), 24-cm field of view, 256 \times 180 matrix before and after intravenous administration of 0.1 mmol/kg of gadolinium-pentetic acid. All examinations covered the brain from the level of the foramen magnum to the higher convexity of the skull, using 3-mm slice thickness and no interslice gap, yielding 44 contiguous images. The number and volume of MS lesions were quantified by the MSAnalyze computerized software as previously described.¹⁶

STATISTICAL ANALYSIS

We calculated that 91 patients would be needed for the study, given an estimated 1-year rate to develop a second attack in the placebo group of 50%,⁷ an absolute effect of treatment of 30%, a 5% probability of a type I error (2-tailed), and a power of 80%. The calculation was adjusted to allow for 10% of the patients to be withdrawn or lost to follow-up before the development of MS. Primary analyses included all randomized patients and followed the intention-to-treat principle. The 2-sample *t* test and nonparametric signed rank test were applied for testing differences between the study groups for quantitative variables. The data on the volume and number of MS lesions on MRI were evaluated by the Mann-Whitney rank sum test. Pearson χ^2 and Fisher exact tests were applied to examine differences between the study groups for the categorical variables.

The Spearman test was used to assess correlations between the study variables. The cumulative probability of developing a second attack within 12 months from study entry was calculated for each group according to the Cox proportional hazards model, with and without covariates (time-dependent, sex, age, MRI variables). Calculations were performed using PROC PHREG in SAS software version 8.2 (SAS Institute, Cary, NC). All tests applied were 2-tailed, and a P value of 5% or less was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS

Figure 1 is a flow diagram illustrating the progress of patients throughout the trial. Ninety-one patients were enrolled in the trial; 45 were randomly assigned to the IVIg treatment group and 46 to the placebo group. The baseline clinical and MRI characteristics of the 2 groups did not differ significantly and are presented in **Table 1**.

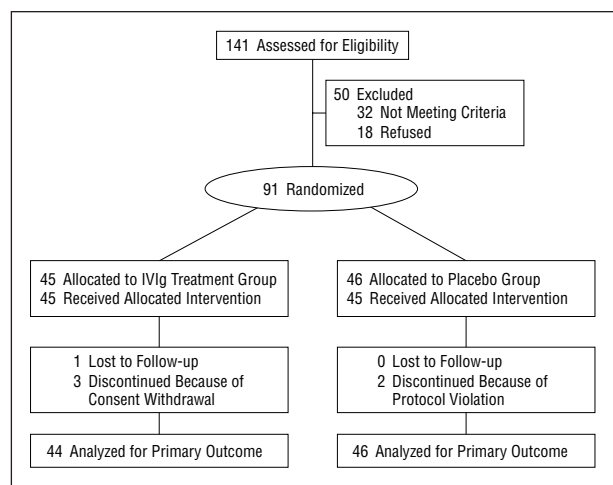


Figure 1. Flow diagram illustrating the progress of patients throughout the trial. IVIg indicates intravenous immunoglobulin.

RATE OF OCCURRENCE OF SECOND ATTACK

The cumulative probability of experiencing a second attack during the first year from onset was significantly lower in the IVIg treatment group as compared with the placebo group (rate ratio, 0.36 [95% confidence interval, 0.15-0.88]; $P = .03$) (**Figure 2**). After adjustment for age, sex, and the number and volume of lesions on T2-weighted brain MRIs, the effect of treatment with IVIg appeared to be stronger (adjusted rate ratio, 0.31 [95% confidence interval, 0.12-0.80]; $P = .02$). At trial completion, the cumulative probability of fulfilling the criteria for the diagnosis of MS was 26% in the IVIg treatment group and 50% in the placebo group ($P = .03$). Thus, IVIg treatment reduced the probability of reaching definite diagnosis by 48%.

BRAIN MRI LESION LOAD

The change in the number and volume of lesions on T2-weighted MRIs and the number and volume of gadolinium-enhancing lesions on T1-weighted MRIs after 12 months of treatment are presented in **Table 2**. The analysis of change for T2-weighted lesions was performed after adjustment for baseline volume and number of lesions. The effect of treatment with IVIg resulted in a significant reduction in the volume and number of T2-weighted lesions as compared with the placebo group ($P = .012$ and $P = .011$, respectively). Similarly, the volume of gadolinium-enhancing lesions at 12 months was lower in the patients treated with IVIg compared with the placebo group (median, 42 mm³ vs 68 mm³, respectively; $P = .03$), suggestive of treatment effect on active inflammation. The mean number of gadolinium-enhancing lesions at 12 months did not differ significantly between groups.

EFFECT OF STEROID TREATMENT AT ONSET

Corticosteroid treatment was given during the first neurological event to 57 patients (62.6%; 28 patients later ran-

Table 1. Baseline Characteristics

	All Patients (N = 91)	Patients Treated With IVIg (n = 45)	Patients Treated With Placebo (n = 46)	P Value
Female, No. (%)	68 (74)	34 (74)	34 (74)	.89
Age, y, mean ± SD	33.9 ± 10.9	33.2 ± 11.6	34.5 ± 10.2	.56
Duration of symptoms prior to treatment, d, mean ± SD	35 ± 16	33 ± 12	38 ± 14	.07
Baseline EDSS score, mean ± SD	2.2 ± 1.1	2.4 ± 1.3	2.0 ± 0.8	.07
T2-weighted lesions				
No. of lesions, mean ± SD	29.8 ± 2.8	29.3 ± 4.1	30.5 ± 3.9	.83
Volume, mm ³				
Median	685	620	765	.31
25th and 75th percentiles	263, 2470	231, 2741	279, 2012	
Gadolinium-enhancing lesions				
No. of lesions, mean ± SD	8.8 ± 6.7	9.2 ± 5.4	8.5 ± 7.6	.65
Median	7.0	8.5	7.0	
Volume, mm ³				
Median	102	104	95	.84
25th and 75th percentiles	53, 190	49, 185	65, 194	

Abbreviations: EDSS, Expanded Disability Status Scale; IVIg, intravenous immunoglobulin.

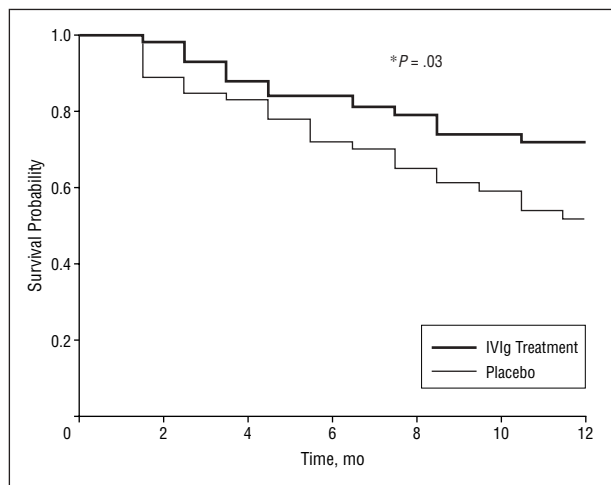


Figure 2. Cox proportional hazards model estimates of the cumulative probability of developing clinically definite multiple sclerosis. A statistically significant difference between groups of $P=.03$ was reached after 8 months.

Table 2. Brain Magnetic Resonance Imaging (MRI) Findings on T2-Weighted and Gadolinium-Enhanced Lesion Load After 12 Months of Treatment

Variable	IVIg Treatment	Placebo	P Value
T2-weighted lesions			
No. of patients	42	45	
Change in volume, mm ³			
Median	-84	38	.012
25th and 75th percentiles	-425, 119	-122, 747	
Mean \pm SD change in No. of lesions	-2.9 \pm 1.9	5.7 \pm 2.6	.011
Gadolinium-enhancing lesions on T1-weighted MRIs			
No. of patients	41	43	
No. of enhancing lesions			
Mean \pm SD	4.6 \pm 5.9	5.6 \pm 5.3	.09
Median	3.0	4.0	
Volume, mm ³			
Median	42	68	.03
25th and 75th percentiles	0, 68	20, 165	

Abbreviation: IVIg, intravenous immunoglobulin.

domized to the IVIg treatment group and 29 later randomized to the placebo group). There was no effect of corticosteroid treatment on the probability of developing a second neurological event in either group ($P=.74$ for the IVIg treatment group; $P=.13$ for the placebo group).

MODELING OF BASELINE VARIABLES

We constructed a hierarchical model to account for the effect of baseline demographic, clinical, and MRI variables on the primary outcome. For purposes of this model, patients' exposure to IVIg was defined as the independent variable while sex, age, EDSS score, T2-weighted lesion volume, gadolinium-enhancing lesion volume, and corticosteroid treatment were defined as the dependent variables (**Table 3**). Except for the highly significant effect of IVIg treatment ($P=.02$), none of the baseline variables affected the primary outcome.

Table 3. Analysis of Odds Ratio Estimates

Parameter	Odds Ratio (Wald 95% Confidence Interval)	P Value
IVIg treatment	3.11 (1.17-8.26)	.02
Sex	0.95 (0.31-2.95)	.93
Age	1.03 (0.98-1.08)	.20
EDSS score	0.59 (0.35-1.02)	.06
T2-weighted lesion volume	1.00 (0.99-1.02)	.18
Gadolinium-enhancing lesion volume	0.98 (0.96-1.02)	.37
Corticosteroid treatment	1.51 (0.51-4.43)	.46

Abbreviations: EDSS, Expanded Disability Status Scale; IVIg, intravenous immunoglobulin.

Table 4. Adverse Events*

Type of Adverse Event	IVIg Treatment	Placebo
Rash	8 (1.4)	5 (1.2)
Headaches	7 (1.3)	9 (2.1)
Nausea	4 (0.7)	3 (0.7)
Dyspnea	5 (0.9)	9 (2.1)
Fever	3 (0.6)	0
Diarrhea	1 (0.2)	0
Palpitations	0	1 (0.2)
Infusion site pain/edema	0	2 (0.5)
Total	28 (5.2)	29 (6.7)

Abbreviations: IVIg, intravenous immunoglobulin.

*Values are expressed as number (percentage) of infusions.

COMPLETENESS OF FOLLOW-UP

One patient in the IVIg treatment group was lost to follow-up within the first week of the study. Thus, the data obtained for this patient was used only for the analysis of baseline parameters. Treatment was discontinued early for a reason other than the development of a second attack in 3 (6.7%) of the 45 patients in the IVIg treatment group because of withdrawal of consent and in 2 (4.3%) of the 46 patients in the placebo group because of protocol violation.

ADVERSE EVENTS

Overall, the incidence of adverse effects judged to be treatment related was low. Nineteen patients in the IVIg treatment group and 21 patients in the placebo group reported at least 1 adverse event. Of the 969 infusions administered throughout the trial, there were 28 (5.2%) of 539 events recorded in the IVIg treatment group and 29 (6.7%) of 430 in the placebo group ($P=.15$). Adverse events in both groups included headaches, rash, nausea, and tightness in the chest; all resolved spontaneously within 24 hours. The adverse events are listed in **Table 4**.

COMMENT

To the best of our knowledge, the current study is the first in the literature to evaluate the effect of IVIg treat-

ment in patients with the first demyelinating event suggestive of MS. The results indicate that IVIg treatment is beneficial for these patients and significantly reduced the rate of a second attack within the first year from onset. Treatment-related decrease in inflammatory disease activity as measured by brain MRI was also demonstrated. Our group has previously shown that IVIg treatment is effective in patients with relapsing-remitting MS as well as in patients with MS during pregnancy and postpartum.^{17,18} Four double-blind trials in patients with relapsing-remitting MS have demonstrated that IVIg treatment reduces the relapse rate and number of gadolinium-enhancing lesions and in this respect seems comparable with established therapies in relapsing-remitting MS (ie, interferon- β and glatiramer acetate). Because of the relatively small sample size of these studies, a meta-analysis was recently undertaken to demonstrate a significant beneficial effect of IVIg treatment on the annual relapse rate (effect size -0.5 ; $P < .001$) as well as on the proportion of patients who were relapse free and the change in neurological disability by EDSS score.¹³ In another small-sample study, quantitative brain MRI analysis showed a statistically significant decrease in the volume of lesions in patients with relapsing-remitting MS treated with IVIg compared with placebo at both the 3- and 6-month follow-ups.¹⁹ Studies of patients with secondary progressive MS failed to demonstrate an IVIg treatment effect on disability, and IVIg treatment failed to improve stabilized visual and motor deficits.²⁰

The suggested mechanisms of action of IVIg treatment that include both anti-inflammatory effects and promotion of remyelination advocate that IVIg treatment could be of benefit in the early stage of MS. Our results indeed support this hypothesis, because we found that IVIg treatment reduced the probability of reaching a definite diagnosis of MS by 48% within the first year from onset. The incidence rate of a second attack within 1 year in the placebo group was 50%, similar to our previously reported rates in untreated patients diagnosed with probable MS.⁷ When computing the effects of baseline variables on the probability of developing a second attack, none of the clinical, demographic, or MRI variables had a significant effect, except for exposure to IVIg treatment, which yielded a significant 3.11-fold effect (odds ratio, Table 3).

Our findings of the automated computerized analysis of brain MRIs¹⁶ provide additional objective support for the clinical primary outcome in the present study and demonstrate that IVIg treatment reduced inflammation and activity of the disease. Treatment was found to be safe with no serious adverse events. Patients tolerated treatment well and adherence to the study protocol was high. To date, there have been 2 large studies that evaluated the effects of treatment with immunomodulatory drugs in the first neurological event suggestive of MS.^{11,12} In the first study,¹² it was shown that fewer patients who were treated with interferon β -1a developed clinically definite MS as compared with patients treated with placebo (34% vs 45%; $P = .047$). The number of new T2-weighted MRI lesions and the increase in lesion burden were significantly lower with active treatment.¹¹ In the second study, it was again shown that the cumulative

probability of developing clinically definite MS was lower in the interferon β -1a group as compared with the placebo group (rate ratio, 0.56; $P = .002$). Patients in the interferon β -1a group had a relative reduction in the volume of brain lesions and fewer gadolinium-enhancing lesions.¹² Both studies suggested that initiating treatment with interferon β -1a early, at the time of the first demyelinating event, is beneficial for patients with probable MS. Because our study methods and inclusion criteria differed from the previously mentioned studies, comparison should be carefully undertaken.

Our results, although based on a small sample size and of a relatively short duration of treatment, show that IVIg treatment in patients with the first demyelinating attack has beneficial effects on the rate of developing a second attack and on the dissemination of the disease as demonstrated by T2-weighted and gadolinium-enhanced MRI lesion load. The baseline mean number of gadolinium-enhanced lesions was relatively high, and this can be explained by the fact that only 62.6% of patients were treated with steroids, as well as by the high sensitivity of the MSAnalyze computerized software to identify lesions. Treatment effect was found for the volume but not for the number of enhancing lesions. The appearance of new lesions might suggest that 1 year of IVIg treatment was not sufficient to eradicate disease activity. However, treatment had succeeded in limiting and reducing the volume of gadolinium-enhancing lesions as compared with the untreated placebo group.

We conclude that treatment with IVIg could be considered as a treatment option in patients with the first demyelinating event suggestive of MS. More so if treatment options with β interferons cannot be offered because of intolerance, unwillingness to take injectable medications, or patients' desire to become pregnant. Future studies evaluating the combined effects of IVIg treatment with β interferons or glatiramer acetate may offer an additive favorable effect on the occurrence of second attack.

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Additional information: All authors had full access to all the data and had the right to publish all the data. The data were analyzed by an independent statistician (Gil Harrai, Medistat, Raanna, Israel).

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