Intravenous immunoglobulin treatment in multiple sclerosis

Effect on relapses

A. Achiron, MD, PhD; U. Gabbay, MD; R. Gilad, MD; S. Hassin-Baer, MD; Y. Barak, MD; M. Gornish, MD; A. Elizur, MD; Y. Goldhammer, MD; and I. Sarova-Pinhas, MD

Article abstract—We conducted a double-blind, placebo-controlled study of 40 patients (aged 19 to 60 years) with clinical definite relapsing remitting (RR) MS and brain MRI confirmed. Patients were randomly assigned to receive a loading dose of immunoglobulin IgG (0.4 g/kg/body weight per day for 5 consecutive days), followed by single booster doses (0.4 g/kg/body weight) or placebo once every 2 months for 2 years. The primary outcome measures were change in the yearly exacerbation rate (YER), proportion of exacerbation-free patients, and time until first exacerbation. Neurologic disability, exacerbation severity, and changes in brain MRI lesion score were the secondary outcome measures, all determined at baseline, 1 year, and on completion. Treated patients showed a reduction in YER from 1.85 to 0.75 after 1 year and 0.42 after 2 years versus 1.55 to 1.8 after 1 year and to 1.4 after 2 years in the placebo group ($p = 0.0006$, overall), reflecting a 38.6% reduction in relapse rate. Six patients in the IVIg group were exacerbation free throughout the 2-year period of the study, whereas none were exacerbation free in the placebo group. The median time to first exacerbation was 233 days in the IVIg group versus 82 days in the placebo group ($p = 0.003$). Neurologic disability as measured by the Expanded Disability Status Scale (EDSS score) decreased by 0.3 in the IVIg group and increased by 0.15 in the placebo group. Total lesion score evaluated by brain MRI did not show a significant difference between groups. Side effects were minor and occurred in only 19 of 630 (3.0%) infusions administered in both groups. Our results suggest that IVIg may be safe and effective in reducing the frequency of exacerbations in RR-MS.

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Relapsing-remitting (RR) MS is characterized by the appearance or worsening of neurologic symptoms.[1] The yearly exacerbation rate (YER) in these patients is the main factor affecting neurologic disability and quality of life, because additional relapses the probability of complete clinical remission decreases.[2]

To alter the course of the disease and ultimately arrest progression, immunomodulating drugs are being widely researched.[3-7] Intravenous immunoglobulin (IVIg) was shown to be beneficial in the treatment of several immune regulation disorders.[8,9] In earlier uncontrolled studies, IVIg has been used in the treatment of acute exacerbation of RR-MS,[10-12] with encouraging results. A previous open-controlled study in 20 RR-MS patients treated with IVIg for 3 years demonstrated a significant decrease in YER.[13,14] The aim of the present study was to conduct a randomized double-blind, placebo-controlled trial to evaluate the effects of IVIg treatment on the course of RR-MS.

Methods. *Eligibility of patients.* One hundred sixty-four patients suffering from MS were referred for initial evaluation by several nationwide neurologic centers. Of these, 40 were enlisted according to the following criteria. Inclusion criteria were clinically definite RR-MS[15] of more than 1-year duration, average YER during the 2 years preceding the study of 0.5 to 3, EDSS[16] score of 0 to 6.0, and age range 18 to 60 years. Exclusion criteria were patients with secondary progression disease course, serum immunoglobulin (IgA) deficiency, long-term steroids or cytotoxic medication treatment 12 months before the study, major psychiatric disorder, and major cognitive impairment. Patients received a detailed explanation, and all signed a written informed consent. The study was approved by the ethical committee of each participating medical center and by the Ethical Committee of the Israeli Ministry of Health.

Study design. A double-blind, placebo-controlled protocol specified IV administration of immunoglobulin (Bayer, Promedico, Israel) at a loading dose of 0.4 g/kg/body weight per day for five consecutive days or placebo consisting of 0.9% saline. Additional booster doses of IVIg 0.4 g/kg/body weight or placebo were administered once daily every 2 months for 2 years. The use of saline as a placebo was preferred to avoid nonspecific protein effect. Taking into account the different physical properties of the two solutions and the theoretic possibility of identifying the solutions by physical means such as heating, electrophoresis,

From the Multiple Sclerosis Center (Dr. Achiron); the Gertner Institute of Epidemiology and Health Policy Research (Dr. Gabbay); the Department of Neurology (Drs. Hassin-Baer and Goldhammer), Sheba Medical Center, Tel Hashomer; the Department of Neurology (Drs. Gilad and Sarova-Pinhas), Edith Wolfson Medical Center, Holon; the Abarbanel Mental Health Center (Drs. Barak and Elizur), Bat Yam; and the Department of Radiology (Dr. Gornish), Beilinson Medical Center, Petah Tikva. All affiliated to the Sacker Faculty of Medicine, Tel Aviv University, Israel.

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Address correspondence and reprint requests to Dr. A. Achiron, Multiple Sclerosis Center, Sheba Medical Center, Tel Hashomer, 52621, Israel.

or whipping, considerable precautions were taken to ensure blindability. Patients were assigned to receive immunoglobulin or placebo by a block-stratified randomization procedure designed to ensure groups balanced for YER, age, and disease duration. The code was not broken until all patients completed the study. All patients and evaluators were blinded to treatment. Randomization was performed at the pharmacy, and the bottles of immunoglobulin or placebo were wrapped in sealed opaque bags and brought to the patients' rooms. The entire IV set was covered by an opaque plastic bag to ensure that any possible fluid turbidity or frothing would not be evident to the investigators or patients. Upon entry, and monthly thereafter, every patient underwent a neurologic examination by two examining neurologists, and an independent EDSS score was recorded by each. Mean score was used in the final statistical analysis. Neuropsychiatric evaluation and a brain MRI were performed before the study, after 1 year and 2 years. Routine blood chemistry, CBC, serum immunoglobulin levels, and an immunologic profile were determined at baseline and every 6 months.

Assessment. A relapse was defined as the rapid appearance, reappearance, or worsening of one or more neurologic abnormalities, persisting at least 48 hours, after a relatively stable or improving neurologic state of at least 30 days. A relapse was confirmed only when the patient's symptoms were accompanied by objective changes on neurologic examination by the treating neurologist who was blind to the patient's treatment. Patients presenting fever accompanied by exacerbation were excluded from definition of relapse. Neurologic disability was scored according to the Kurtzke EDSS. Exacerbation severity was graded as follows: mild, a change in one grade in the score for one of eight functional scores of the Kurtzke EDSS; moderate, a change in two grades in the score for one of eight functional scores of the EDSS or change in one grade in the score for two of eight functional groups; and severe, a change in two grades in the score for at least two of eight functional scores of the EDSS. Severe and moderate exacerbations in either group were treated with IV methylprednisolone (1 g/day) or oral prednisone (60 mg/day) for 5 consecutive days, respectively. Mild exacerbations were not treated.

Distribution of cumulative disability (deterioration, stability, improvement) over time was defined as a change of at least one point in the EDSS score compared with baseline. Computerized calculation assuming linear change between two consecutive EDSS score measurements was used for each time interval.

Neuropsychiatric evaluation was performed by a psychiatrist. Each patient underwent a semistructured psychiatric interview and scored on a battery of five neuropsychological measures covering anxiety, depression, cognition, and general psychopathology.

Brain imaging was performed on a 0.5-T superconductive magnet system (Gyrex V, Elscint, Israel). Spin-echo T1-weighted scans were obtained in the sagittal plane with a TR of 400-600 msec and TE of 20 msec. Patients were positioned using a standardized protocol to determine the angle of alignment for subsequent MRI examinations. Spin-echo proton density and T2-weighed sequences were performed using TR of 3,000 and TE of 20 and 80 msec, a 5-mm slice thickness, and a 1-mm gap between slices. All scans were scored by a neuroradiologist blinded to the patients treatments. Briefly, as previously described,[17] MRI score was based on the number and diameter of demyelinating plaques. The median diameter value was established and the area of the circle with this diameter was calculated. Then, the calculated area was multiplied by the mean number of lesions, and this yielded a combined score between 0 (no lesions) and 10 (maximal involvement).

Table 1 *Demographic and baseline clinical disease characteristics of the study patients*

Variable	IVIg* (n = 20)	Placebo* (n = 20)	*p* Value
Female/male	16/4	16/4	
Age (y)	35.4 ± 2.1	33.8 ± 2.4	0.62
Disease duration†	4.10 ± 0.61	3.95 ± 0.64	0.86
YER‡	1.85 ± 0.26	1.55 ± 0.17	0.34
Baseline EDSS	2.90 ± 0.43	2.82 ± 0.37	0.89
Baseline MRI	3.21 ± 0.53	3.04 ± 0.54	0.82

* Values are means ± SEM.
† Time since definite diagnosis.
‡ Mean for the 2 years before the study.

YER = yearly exacerbation rate; EDSS = Expanded Disability Status Scale.

Outcome measures. The primary end points of the study were YER, proportion of exacerbation-free patients, and time until first exacerbation. Secondary outcome measures were exacerbation severity, neurologic disability (EDSS and distribution of cumulative disability over time), and annual brain MRI score.

Sample size and power. Stratified randomization (based on YER in the 2 years before the study, age, and disease duration) was used to assign patients to treatment groups. Sample size was calculated according to the following assumptions: mean YER = 2, SD of YER estimated as 1.5, $p = 0.05$ (one tail), and power = 80%.

Under the assumption of 50% expected reduction in YER, 14 patients were the minimum sample size per group; with 33% reduction in YER, the minimum size was 38 patients per group. Taking into consideration a 30% dropout rate, we thus included 20 patients in each group.

Statistical analysis. The following statistical models were used in the study: YER comparison, *t*-test; changes in YER, paired *t*-test; proportion of exacerbation-free patients, Fisher's exact test[18]; remission interval distribution, survival analysis by Kaplan-Meier[19]; exacerbation severity comparison, *t*-test; change in EDSS, paired *t*-test; distribution of cumulative disability over time, chi-square test; and annual MRI score, paired *t*-test. Analysis of data included only patients that completed the 2-year study period. We also did an analysis by intention to treat that included the two patients who completed only the first year of the study.

Results. Baseline clinical and demographic characteristics in the two treatment arms, after randomization, are presented in table 1. The two groups were statistically comparable on all parameters.

Effect of IVIg on primary outcome measures. Efficacy results for the study's first year, second year, and the total

Table 2 Effect of IVIg on YER

	IVIg	Placebo	*p* Value
Pre-entry YER	1.85 ± 0.26	1.55 ± 0.17	0.34
First year	0.75 ± 0.16*	1.8 ± 0.2†	0.0002
Second year	0.42 ± 0.14*	1.42 ± 0.23†	0.0009
YER: 2-year data	0.59	1.61	0.0006

* $p < 0.05$ compared with baseline.
† Not significant.

YER = yearly exacerbation rate.

period (2 years) are presented in table 2. Exacerbation rate in the first year was 0.75 in the IVIg-treated group versus 1.80 in the placebo group ($p = 0.0002$). In the second year, rates were IVIg, 0.42 versus placebo, 1.42, ($p = 0.0009$). Annualized exacerbation rate demonstrated a 38.6% reduction in the IVIg-treated group compared with 4.2% in the placebo group ($p = 0.0006$). The number of exacerbation-free patients was 8 in the IVIg group versus 1 in the placebo group during the first year, and 12 in the IVIg group versus 3 in the placebo group in the second year. Six patients in the IVIg group were exacerbation free throughout the 2-year period of the study, whereas none were exacerbation free for the whole trial period in the placebo group (table 3). Kaplan-Meier analysis showing the probability of remaining exacerbation-free throughout the study is presented in the figure. The log-rank statistic used to test comparability for each treatment group demonstrated that the median time to first exacerbation was 233 days in the IVIg group compared with 82 days in the placebo group ($p = 0.003$). Because higher relapse rates were observed in the placebo group, these patients received more corticosteroid treatments during the study period. When intent-to-treat analysis was performed, including the two patients who did not complete the trial, the YER in the second year was 0.4 in the IVIg group and 1.54 in the placebo group ($p < 0.001$).

Effect of IVIg on secondary outcome measures. There was no significant change in the mean EDSS by treatment arm, although a trend toward reduced neurologic disability was observed in the IVIg group (baseline EDSS = 2.90 ± 0.43 and study completion EDSS = 2.60 ± 2.02), whereas a minor increase occurred in the placebo group (baseline EDSS = 2.82 ± 0.37 and study completion EDSS = 2.97 ± 1.47). There was a significant difference in the distribution of neurologic disability over time between the two groups. The proportion within each group who improved was 23.5%, remained stable was 62.8%, or worsened was 13.7% in those receiving IVIg compared with 10.8% (improved), 72.1% (stable), and 17.1% (worsened) in the placebo group ($p = 0.03$).

Table 3 Effect of IVIg on exacerbation-free patients

	IVIg	Placebo	*p* Value
First year	8	1	0.001
Second year	12	3	0.001
Total study period	6	0	0.001
Median time to first exacerbation (days)	233	82	0.003

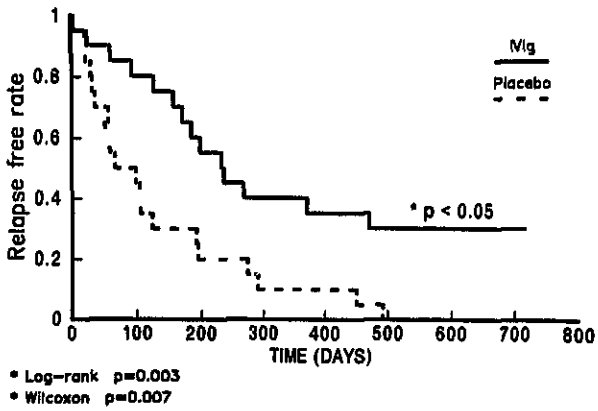

Figure. Kaplan-Meier analysis showing the probability of remaining exacerbation free during the 2-year study period.

The mean annual severity of exacerbations in the IVIg versus placebo groups during the first and second year were not significantly different (1.62 versus 1.82 in the first year and 2.28 versus 2.19 in the second year, respectively). At the end of the first year, mean MRI lesion score in relation to baseline increased by 11.8% in the IVIg group and increased by 29.6% in the placebo group. However, at the end of the second year, 10 patients were unavailable for MRI examination: 3 in the IVIg group and 7 in the placebo group. Unavailability was due to the follow ing reasons: dropout, 2; pregnancy, 4; and noncompliance, 4.

Analysis of MRI lesion scores at the end of the study revealed nonsignificant differences. Mean MRI score increased to 3.59 ± 0.47 in the IVIg group and to 3.94 ± 0.77 in the placebo group ($p = 0.7$) at the end of the first year of the study. Upon study completion, mean MRI scores were 3.82 ± 0.6 in the IVIg group and 3.2 ± 0.76 in the placebo group ($p = 0.51$). In 12 patients, brain MRI scores improved after 2 years; 8 of 12 were in the IVIg treatment group.

No significant changes were found in neuropsychologic measures used. In the IVIg group, one patient developed clinically overt depression requiring antidepressant treatment. In the placebo group, 2 patients developed a hypomanic episode.

Withdrawals, adverse events, and side effects. Two patients discontinued treatment after the first year (one in each group). One patient chose to participate in a different drug trial and the other withdrew due to patient-perceived worsening. There were no hematologic or biochemical blood laboratory test abnormalities associated with IVIg treatment. Overall, incidence of notable side effects was low. Of the 630 infusions administered throughout the trial, there were 12 of 316 (3.8%) events recorded in the IVIg group and 7 of 314 (2.2%) in the placebo group ($p < 0.05$). Patients tolerated immunoglobulin infusions well. Side effects in both groups included fatigue, headaches, rash, and low-grade fever, all spontaneously resolved within a few hours.

Blindability questionnaire. Upon completion of the study, all patients were requested to complete a short questionnaire focusing on subjective assessment of treatment. Each patient marked the treatment she or he be-

Table 4 Evaluation of patient's blindability questionnaire

	Actual treatment		
	IVIg	Placebo	
Patient's belief			
IVIg	7	13	20
Placebo	12	6	18
	19	19	

lieved she or he had received during the study. The results of the questionnaire are presented in table 4. Positive predictive value was 35% (7/20), negative predictive value was 33% (6/18), sensitivity was 36.8% (7/19), and specificity was 31.6% (6/19). Patient ability to perceive correctly the treatment they received was low, hence validating their blindability. The degree of physician blinding was not evaluated.

Discussion. The results of the present study suggest that IVIg is a safe and effective treatment for RR-MS. Although our results support previous studies reporting beneficial effect of IVIg in reducing the relapse rate in RR-MS patients,[13,14] there is a need for additional studies, using larger numbers of patients for definite confirmation. Major improvement in objective primary outcome measures—YER, proportion of exacerbation-free patients, and time until first exacerbation—were highly significant. The validity of the results is strengthened by the balanced randomization, double-blind study design, and the use of strict and unbiased criteria to define all outcome measures.

The natural course of RR-MS is characterized by YER ranging from 0.85 to 1.15 in the remitting stage.[20,21] Although some patients recover after each relapse, in many recovery tends to be incomplete after some exacerbations, resulting in varying degrees of disability. Many of these patients subsequently enter a progressive phase of the disease associated with increased handicap.[22] Thus, clinical trials in MS are mainly aimed at induction and maintenance of remission and improvement of neurologic disability. The ability of IVIg to alter the course of the disease was highly significant in the present study, wherein patients with relatively high YER were included. The data indicate a reduction of 68% in YER in the first year compared with baseline for the IVIg group. This effect was highly associated with duration of treatment course or a cumulative effect, as reflected by the reduction of 77.3% in attack rate during the whole study period resulting in an annualized attack rate reduction of 38.6%. Recently, Fazekas et al.[23] reported the results of IVIg treatment in a 2-year randomized, double-blind, placebo-controlled study of 148 RR-MS patients. Similarly to our results, annual relapse rate reduction by active treatment over placebo was 59%, and the percentage of relapse-free patients was significantly higher in the IVIg-treated patients.

In the natural course of MS, neurologic disability scored by the EDSS is estimated to deteriorate by 0.3 points annually.[20] In our study, the mean EDSS score at 2 years compared with baseline for the IVIg-treated group showed minor reduction (0.3), whereas the placebo group showed minor increased disability (0.15), both not statistically significant. Distribution of disability over time showed that IVIg treated patients spent significantly more time in improved or stable neurologic status in comparison with the placebo group, suggesting a better quality of life for the IVIg patients during remission. Hence, detecting IVIg effects on neurologic disability calls for longer treatment duration and possibly larger groups of patients, as demonstrated by Fazekas et al.[23]

In RR-MS patients, up to 20 new lesions may appear in 1 year.[24] Nevertheless, individual brain MRIs do not correlate well with clinical disability as measured by neurologic scales.[25] In the present study, the annual disease burden provided a "snapshot in time," measuring total lesion area by the objective quantitative approach analysis. However, recently accumulated data indicate that monthly scanning of the brain with T2 and gadolinium-enhanced T1-weighted MRI is preferred and provides a sensitive monitoring of the disease activity.[26] Thus, in the present study, the MRI results may not be sufficient to reliably interpret the disease process as the use of yearly T2 lesion load, as an outcome measure, is now known to be insufficient. Additional factors such as measurements errors, measurements drift, and undetectable small lesions due to availability of a 0.5-T magnet all contribute to an insensitive measurement. It is worthy to note that the sample size in our study was established with a focus on expected major YER reduction; thus, MRI measurements not a priori planned for may have escaped statistical detection.

Among the postulated immunomodulating actions of IVIg, several are relevant to MS. IVIg can prevent the autoimmune reaction by blocking Fc receptors, detected in activated T cells,[27,28] and in CNS perivascular macrophages, microglia, and endothelial cells.[29] IVIg can also inhibit the effector functions of activated T cells and the release of cytokines and lymphokines.[30,31] Apart from its immunomodulating effects, IVIg was reported to enhance CNS remyelination[32] after penetration of the blood-brain barrier. Blood-brain barrier disruption is not a prerequisite for IVIg effectiveness. With an intact blood-brain barrier, raising the IgG serum concentration from the average value of 10 to 30 g/L will increase CSF concentration from approximately 25 to 65 mg/L.[33] This ability of IVIg to penetrate the intact blood-brain barrier contributes to enhanced remyelination and enables active involvement of the drug even during remissions.

Consequently, the administration of IVIg during the RR course of MS can arrest the ongoing autoimmune inflammatory process through influence at various independent pathways. After suppression of

active immune process, the treatment may contribute to reduction of long-term disability by promoting remyelination.

IVIg treatment was associated with few and minor side effects and is safe during pregnancy, which is an important consideration in choosing treatment modality in a disease affecting mainly young women during the reproductive years.[34] IVIg has a significant benefit in reducing exacerbations in RR-MS patients and hence should be considered as a relapse-preventing therapy.

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