# Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis

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**Article abstract**—We wanted to assess whether *intravenous immunoglobulin G* (IVIG) decreases disease activity on MRI in relapsing MS. Previous trials of IVIG in relapsing-remitting MS demonstrated a reduction of acute relapses, but these studies did not include MRI. We treated 26 patients in a randomized, double-blind, crossover study of IVIG 1 g/kg daily or placebo on 2 consecutive days every month during two 6-month treatment periods. The primary end point was the number of gadolinium-enhancing lesions on monthly serial MRI. Secondary efficacy variables were the occurrence of exacerbations, clinical neurologic ratings, total MS lesion load on T2-weighted MRI, and multimodal evoked potentials. Eighteen patients completed the entire trial; eight patients did not. Twenty-one patients completed the first treatment period and at *least two MRI examinations in the second* treatment period and were included in the intention-to-treat analysis. On serial MRI, we observed fewer enhancing lesions per patient per scan during IVIG treatment (median, 0.4; range, 0 to 9.3) than during placebo treatment (median, 1.3; range, 0.2 to 25.7; $p = 0.03$). During IVIG treatment, 15 patients were exacerbation free compared with only 7 on placebo ($p = 0.02$). The total number of exacerbations in the IVIG period was 11 and in the placebo period, 19 (not significant). None of the remaining secondary efficacy measures were significantly different between the two treatment periods. The number of adverse events, in particular eczema, was significantly higher during IVIG therapy than during placebo treatment. These results suggest that IVIG treatment is beneficial to patients with relapsing MS.

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Intravenous immunoglobulin G (IVIG) has been shown to be effective in the treatment of a number of immune mediated diseases, including neurologic disorders characterized by demyelination in the peripheral nervous system (i.e., Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy).[1-3] The mechanisms of IVIG benefit are not fully understood and may be different in each disorder. IVIG produced from large plasma pools contains a variety of anti-idiotypic antibodies that may neutralize circulating autoantibodies against myelin proteins,[4] restore the physiologic pattern of spontaneous fluctuations in the concentration of autoantibodies in plasma,[5] and down-regulate production[6] or neutralize inflammatory cytokines.[7] Further, IVIG can induce functional blockade of Fc receptors on macrophages,[8] suppress inducer T cells and B cells,[9,10] and inhibit damage of myelin by activated complement.[11] Moreover, in animal models of demyelinating disorders, IVIG promotes remyelination.[12-14] Hence, IVIG has the potential to modify and/or reverse a number of the immunologic abnormalities found in MS.

During the last 30 years, a number of small uncontrolled trials have been published using small doses of gamma globulins for the chronic treatment of MS. Most of these studies claimed a beneficial effect of IVIG.[15-17] Higher doses of IVIG were effective in the prevention of acute exacerbations in an open-label study.[18] Recently, a randomized, double-blind study of IVIG in relapsing-remitting MS has demonstrated a reduction of acute relapses, but this study did not include MRI.[19]

In 1992 we initiated a double-blind, placebo-controlled, crossover study of 26 patients with relapsing-remitting or secondary progressive MS with relapses (relapsing-progressive) using frequent gadolinium-enhanced MRI for the evaluation of treatment effect and the occurrence of gadolinium-enhancing lesions as the primary end point.

**Methods.** *Patient population.* The inclusion criteria were relapsing-remitting or secondary progressive MS with relapses (relapsing-progressive MS)[20]; age between 18 and 50 years; disease duration not longer than 10 years;

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***Table 1*** *Baseline characteristics for the two treatment groups*

| | Sequence IVIG-placebo | Sequence placebo-IVIG | *p* Value* |
|---|---|---|---|
| Sex | 4M, 9F | 5M, 8F | NS |
| Age†, y | 31 (23–38) | 39 (25–48) | 0.004 |
| MS duration†, mo | 34 (12–127) | 81 (19–114) | 0.04 |
| EDSS† | 3.5 (2.0–5.5) | 4.5 (3.0–7.0) | 0.006 |
| No. gadolinium-enhancing lesions | | | |
| Mean ± SD | 4.1 ± 9.1 | 3.2 ± 5.1 | NS |
| Median (range) | 1 (0–34) | 1 (0–18) | NS |
| T2 lesion area, $mm^2$† | 1,721 (699–13,546) | 2,583 (140–12,291) | NS |
| Median central motor conduction index (z score) | 5.13 | 17.58 | 0.05 |

* Mann-Whitney *U* test.
† Values are medians with ranges in parentheses.

IVIG = intravenous immunoglobulin G; NS = not significant; EDSS = Expanded Disability Status Scales.

Expanded Disability Status Scale (EDSS)[21] score between 2.0 and 7.0; two or more acute exacerbations in the last year before entry documented from chart review; at least five cerebral lesions on T2-weighted images on a screening MRI; no acute exacerbation within 1 month before inclusion; no corticosteroids during the last 3 months before entry; and no prior treatment with azathioprine, cyclophosphamide, or any other immune modulating treatment at any time.

We excluded women who were pregnant or lactating or who were unwilling to practice an acceptable form of contraception during the study period; patients with other diseases of the CNS or the peripheral nervous system; patients with diseases of the liver, kidney, or blood; patients with immune deficiencies; and patients who could not be exposed to MRI because of metal implants or claustrophobia.

*Treatment regimens.* The trial was conducted as a randomized crossover study. One group was first treated with IVIG for 6 months (1 month = 4 weeks). After a 3-month washout period, patients were then treated with placebo for 6 months. The second group was treated in reverse order. IVIG treatment was administered as infusions of 1.0 g/kg/day for 2 consecutive days at monthly intervals. A monthly dose of 2.0 g/kg is the conventional dose used in other neuroimmunologic disorders such as Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. We too administered this dose in 2 consecutive days because of convenience to the patients and the dosing regimen had been well tolerated in children with Kawasaki syndrome. The IVIG preparation was Gammagard (Baxter Health Care, Hyland Division; Glendale, CA) until April 1994, when this preparation was withdrawn from the market and replaced with Gammagard S/D, which was used thereafter. Placebo treatment consisted of human albumin 2% administered with an identical regimen. Human albumin was chosen as placebo for the purpose of maintaining the blind nature of the trial. To ensure the integrity of the blinding, all IVIG and albumin solutions were prepared in the hospital pharmacy and the container and infusion tubes were covered with red plastic wrappers.

*Conduct of the study.* All patients underwent a pretreatment screening: a clinical neurologic examination including the Scripps Neurological Rating Scale (NRS)[22] and Kurtzke's EDSS,[21] a gadolinium-enhanced MRI of the brain, neurophysiologic examinations with multimodal evoked potentials, and laboratory investigations.

After randomization, patients were examined monthly and whenever an exacerbation occurred using clinical scores (NRS and EDSS). An exacerbation was defined as the appearance of new symptoms or worsening of an old

***Table 2*** *Total number of gadolinium-enhancing lesions in per-protocol group (n = 18) for the treatment sequence IVIG-placebo and the treatment sequence placebo-IVIG*

| | Month 0 (baseline) | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6 | Months 1–6 Total |
|---|---|---|---|---|---|---|---|---|
| Group 1 (n = 9) | | | | | | | | |
| IVIG months 0–6, placebo months 9–15 | | | | | | | | |
| Mean ± SD | 5.2 ± 10.9 | 3.3 ± 4.4 | 1.6 ± 2.1 | 1.6 ± 1.6 | 1.4 ± 2.7 | 1.9 ± 2.4 | 3.3 ± 7.2 | 11.3 ± 17.5 |
| Median (range) | 1 (0–34) | 0 (0–12) | 1 (0–6) | 2 (0–5) | 0 (0–8) | 1 (0–7) | 1 (0–21) | 3 (1–56) |
| Group 2 (n > 9) | | | | | | | | |
| Placebo months 0–6, IVIG months 9–15 | | | | | | | | |
| Mean ± SD | 1.9 ± 3.0 | 1.3 ± 1.9 | 1.9 ± 2.4 | 1.6 ± 2.4 | 1.2 ± 1.6 | 1.6 ± 3.0 | 1.3 ± 1.2 | 8.4 ± 9.4 |
| Median (range) | 1 (0–8) | 1 (0–6) | 1 (0–6) | 1 (0–6) | 1 (0–5) | 0 (0–9) | 1 (0–4) | 5 (1–28) |

IVIG = intravenous immunoglobulin G.

symptom accompanied by signs of neurologic dysfunction attributable to MS and lasting more than 24 hours. Corticosteroid treatment for severe exacerbations was permitted at the discretion of the treating physician. A severe exacerbation was defined as acute symptoms causing functional disability and was treated with IV methylprednisolone 1 g daily for 3 days.

Magnetic resonance imaging was performed before the start of each treatment period and every month during both treatment periods. In case of a clinical relapse, if possible, the patient was referred to an additional MRI before any corticosteroid treatment or the following scan was postponed until at least 3 weeks after the steroid therapy. At each scan, the patient was positioned using external landmarks to ensure reproducible slice positions. Imaging was performed using a 1.5-T Siemens (Erlangen, Germany) Magnetom SP63 MRI scanner. Images in the transverse plane were obtained with a double spin-echo sequence (TR = 2,500 msec, TE = 15 and 90 msec, 1 acquisition, 256 × 256 matrix, 4-mm slice thickness, no interslice gap, 30 slices), thus providing a proton and a T2-weighted image. Further, a T1-weighted sequence (TR = 520 msec, TE = 15 msec, 2 acquisitions) was applied with 30 slices at an identical position as the double spin-echo sequence. Subsequent to contrast agent injection (gadolinium-DTPA [Schering; Berlin, Germany] 0.1 mM/kg body weight), a 10-minute interval was interposed and the T1-weighted sequence was repeated. All scans were evaluated blindly by two independent neuroradiologists. Area measurements were obtained from the T2-weighted sequence images with the proton density images serving as additional templates for the plaque identification. Images were transferred from the Siemens imaging system (a VAX computer system) to an in-house developed software program. Areas were measured by outlining the individual plaques and then adding the pixel counts from all slices of the cerebrum in which plaques were identified. The conversion factors between pixel sizes and areas in square millimeters were known. The areas of the lesions in all slices were summed as a measure of the total lesion area.

Multimodal evoked potentials were performed at the beginning and end of each treatment period and included motor evoked potentials (MEP), visual evoked potentials (VEP), brainstem auditory evoked potentials (BAEP), and somatosensory evoked potentials (SSEP). The methods were previously described in detail.[23,24] MEPs were recorded bilaterally from the brachial biceps, the radial carpal flexor, the first dorsal interosseus muscle of the hand, and the anterior tibial and the abductor halluces muscles. Central motor conduction times (CMCT) were calculated as the difference between the MEP latencies after stimulation of the cortex and the spinal root. A central motor conduction index (CMCI) was calculated as the average deviation from the mean for the 10 muscles studied:

$$\mathrm{CMCI} = \frac{1}{10} \sum_{i=1}^{i=10} \frac{(\mathrm{CMCT_i} - \mathrm{CMCT_m})}{\mathrm{CMCT_m}}$$

in which $\mathrm{CMCT_i}$ is the central motor conduction time observed for the individual muscle and $\mathrm{CMCT_m}$ is the mean value of age-matched healthy control subjects. The indices were expressed as z scores, that is, the difference between the individual patient index and the mean index of the control subjects divided by the SD. The main advantages of z scores are that the conduction indices are directly comparable between individuals of different height and that it gives, as a single number, the information needed to evaluate the individual's deviation from the mean and the limits of normality. The 99% confidence limit of the CMCI intertest variation is 2.0 (z score). z Score indices were calculated for each EP modality using the same equations as for the CMCI. From the P100 latency from each eye to the left and right occipital lobe, a VEP index was calculated. A central sensory conduction index was calculated from the four central conduction times (left and right median and tibial nerve SSEP). For further details, see Ravnborg et al.[24] The results were examined in a blinded manner by a trained neurophysiologist who was unaware of the treatment of the patients.

Laboratory examinations for patient safety were made at the beginning and at the end of each treatment period and comprised hemoglobin; WBC count; platelet count; albumin; IgA; IgG; IgM; M-component; ANA; anti-HIV; hepatitis B and C serologies; screening coagulation tests; alanine-amino-transaminase; alkaline phosphatase; lactate dehydrogenase; plasma electrolytes; plasma creatinine; and urine analysis for blood, protein, and glucose. Toxicity was graded according to World Health Organization recommendations for grading of acute and subacute toxicity.[25] A lumbar puncture (LP) was performed at the

| Month 9 (baseline) | Month 10 | Month 11 | Month 12 | Month 13 | Month 14 | Month 15 | Months 10–15 Total |
|---|---|---|---|---|---|---|---|
| 5.6 ± 12.7 | 7.1 ± 13.2 | 5.0 ± 8.3 | 3.9 ± 6.7 | 6.2 ± 10.8 | 2.7 ± 3.9 | 4.8 ± 6.3 | 29.4 ± 48.2 |
| 1 (0–39) | 3 (0–42) | 3 (0–27) | 2 (0–21) | 2 (0–34) | 1 (0–12) | 2 (0–18) | 9 (2–154) |
| 1.1 ± 8.0 | 0.4 ± 0.5 | 0.1 ± 0.3 | 0.4 ± 1.3 | 0 ± 0 | 0.3 ± 0.7 | 0.8 ± 1.2 | 2.1 ± 2.8 |
| 1 (0–49) | 0 (0–1) | 0 (0–1) | 0 (0–4) | 0 (0) | 0 (0–2) | 0 (0–3) | 1 (0–7) |

beginning and at the end of the treatment and the control periods with examination of the CSF: WBC count, protein and glucose concentration, oligoclonal bands, and IgG index.

*Evaluation of efficacy.* The primary end points were the total number of gadolinium-enhancing lesions on serial MRI and the number of new enhancing lesions. Secondary end points were the percentage of patients with active scans (scans with gadolinium-enhancing lesions), the total lesion load on T2-weighted MRI, changes in multimodal evoked potentials, number of exacerbations, number of exacerbation-free patients, number of severe exacerbations, changes in neurologic function on the NRS, and changes in EDSS ratings.

*Statistical methods.* The statistical analysis of the primary efficacy parameters of the crossover study with two periods was performed by means of the Wilcoxon signed-rank test for pair differences. The McNemar's test (with exact binomial calculations) was applied for the comparison of exacerbation-free patients between the two treatment periods. Examination for period effect was made using the Mann-Whitney test. The number of patients needed to show a reduction of 50% in the main efficacy parameters was 22 given a two-tailed level of significance of 0.05 and a statistical power of 80% (type 2 error, 20%). The analysis of the primary efficacy parameters was performed for all patients who completed the first treatment period and at least 1 month and two MRIs in the second treatment period (i.e., intention-to-treat population) and for all patients who completed both the IVIG and the placebo period (i.e., per-protocol population).

**Results.** *Patient characteristics.* Twenty-six patients, 9 men and 17 women, aged 23 to 48 years (median, 35 years) were included. All had a relapsing course of MS, with 21 relapsing-remitting and 5 secondary progressive MS with relapses (relapsing-progressive disease). The duration of MS disease was 1 to 10 years (median, 5 years). On entry, the median NRS score was 74 (range, 43 to 94) and the median EDSS score was 3.5 (range, 2.0 to 7.0). At baseline, 19 patients showed at least one gadolinium-enhancing lesion on MRI, whereas 7 patients were without enhancing lesions. The median number of gadolinium-enhancing lesions was 1 (range, 0 to 34). The median number of exacerbations during the last year before enrollment was 3 (range, 2 to 10). Patients treated with the sequence placebo-IVIG were significantly older, had longer disease duration, higher EDSS score, and longer CMCTs than patients treated with the sequence IVIG-placebo (table 1).

Eighteen patients completed the crossover study and constituted the per-protocol population, whereas 8 patients discontinued the trial, 4 during IVIG treatment and 4 in the placebo period. In all, 21 patients completed at least 1 month of follow-up and two MRIs in the second treatment period and were hence available for the intention-to-treat analysis. Analysis for period effect showed that no carry-over effect was present. Only the analysis of gadolinium-enhancing lesions in the per-protocol population showed an effect of the treatment sequence of IVIG treatment, IVIG being better in the first treatment period ($p = 0.04$) (table 2).

*MRI.* The analysis of the primary end points, the total number and the number of new gadolinium-enhancing lesions on serial MRI, is shown in tables 2 and 3. Only two patients had MRI performed within 4 weeks after IV methylprednisolone: one patient on placebo had an MRI 20 days after and one patient on IVIG had an MRI 2 days after start of corticosteroids. The mean number of new and total gadolinium-enhancing lesions was significantly reduced by approximately 60% during IVIG treatment compared with placebo both in the per-protocol population and in the intention-to-treat analysis ($p < 0.05$ in all cases). The percentage of patients with active scans (scans with gadolinium-enhancing lesions) on monthly serial MRI appears in figure 1. The activity on MRI decreased after 1 month's treatment with IVIG and remained stable during the 6-month treatment period, whereas no changes were observed during the placebo treatment period. In the per-protocol analysis (18 patients), the average percentage of patients with active scans in six monthly serial MRIs was 37% during IVIG compared with 68% on placebo ($p < 0.01$). Four patients (22%) did not have gadolinium-enhancing lesions during the whole IVIG period, whereas no patients were free of new gadolinium-enhancing lesions during placebo treatment. Four patients had a poor response to therapy, defined as more than 50% active scans during IVIG therapy and/or more active scans on IVIG than on placebo. Five patients were not included in the intention-to-treat analysis because they did not complete the first treatment period and at least 1 month and two MRIs in the second; three of these patients discontinued the trial after 4, 6, and 6 months of IVIG treatment, re-

***Table 3*** *Number of gadolinium-enhancing lesions in serial cranial MRI*

| | Intention-to-treat analysis (n = 21) | | | | Per-protocol analysis (n = 18) | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline* | IVIG | Placebo | 2*p* Value† | Baseline* | IVIG | Placebo | 2*p* Value† |
| All lesions | | | | | | | | |
| Mean ± SD | 3.6 ± 7.7 | 1.3 ± 2.3 | 2.9 ± 5.4 | | 3.8 ± 8.3 | 1.2 ± 2.2 | 3.2 ± 5.9 | |
| Median (range) | 1.3 (0–36.5) | 0.4 (0–9.3) | 1.3 (0.2–25.7) | 0.003 | 1.0 (0–36.5) | 0.4 (0–9.3) | 1.3 (0.2–25.7) | 0.03 |
| New lesions | | | | | | | | |
| Mean ± SD | 3.6 ± 7.7 | 1.1 ± 2.0 | 2.2 ± 4.2 | | 3.8 ± 8.3 | 1.0 ± 1.9 | 2.5 ± 4.7 | |
| Median (range) | 1.3 (0–36.5) | 0.4 (0–8.3) | 0.9 (0.2–20.2) | 0.002 | 1.0 (0–36.5) | 0.4 (0–8.3) | 0.9 (0.2–20.2) | 0.01 |

* Average of the two baseline scans before the two treatment periods.
† IVIG vs placebo (Wilcoxon signed-rank test for pair differences).

IVIG = intravenous immunoglobulin G.

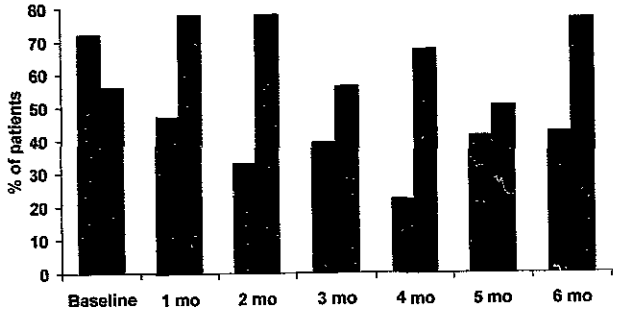


*Figure 1. Percentage of patients with active scans in monthly serial MRI during treatment with intravenous immunoglobulin G (IVIG; gray bars) and placebo (black bars).*

spectively, and had a mean number of gadolinium-enhancing lesions per scan of 0, 0, and 0.7. Two patients discontinued the trial during placebo treatment, one after the first infusion without having an MRI and the other after 2 months, presenting with 3.0 gadolinium-enhancing lesions in one MRI.

No significant differences were found in the secondary MRI efficacy parameter, the total lesion load on T2-weighted MRI (table 4). The median changes in the total lesion area, based on individual patient data, showed a trend toward a reduction during IVIG treatment compared with almost no changes during the placebo period ($p = 0.27$).

*Clinical response.* Table 5 shows the occurrence of acute exacerbations. The number of relapses was 42% lower in the intention-to-treat analysis and 27% lower in the per-protocol analysis during IVIG treatment than in the placebo period, although these differences did not reach statistical significance. Also the number of severe relapses requiring methylprednisolone treatment showed a decreased trend during IVIG treatment. A significantly greater number of patients were relapse free (71%) during the IVIG period than during the placebo period (33%) ($p = 0.02$). During the washout period, five patients experienced relapses, three after placebo treatment and two after IVIG. Two of these relapses, both occurring after the placebo period, were treated with methylprednisolone.

Neither neurologic impairment measured by NRS or disability measured on the EDSS changed significantly from baseline during IVIG or placebo treatment; the mean changes in EDSS during IVIG treatment was 0.0 ± 1.0 and during placebo, 0.2 ± 0.6. Although a greater number of patients improved on IVIG than on placebo (figure 2), no significant differences were found in EDSS changes between the two treatment periods.

*Evoked potentials and CSF findings.* The baseline results of the multimodal evoked potentials showed a significant difference in the CMCI between patients treated with the sequence IVIG-placebo versus patients treated with the sequence placebo-IVIG (see table 1). Comparison of the changes from the beginning to the end of each treatment period showed no significant differences in z scores: ΔVEP was 0.46 during IVIG and 0.86 during placebo, ΔBAEP was −0.25 during IVIG and 0.70 during placebo, ΔSSEP was 0 during IVIG and 0 during placebo, and ΔMEP was −1.07 during IVIG and −0.52 during placebo. A subgroup analysis of patients who were clinically stable (i.e., without acute exacerbation) during IVIG therapy showed an improvement in the CMCI in 10 of 12 patients, whereas 4 of 6 patients who had clinical relapses during IVIG therapy deteriorated in their CMCI. In comparison, 3 of 6 patients without acute exacerbations on placebo showed improvement in the CMCI, whereas 7 of 11 patients who had clinical relapses on placebo deteriorated in their CMCI.

The baseline spinal fluid studies showed oligoclonal bands in all patients and elevated CSF IgG concentration and IgG index in all but two patients; the median value of the CSF IgG concentration was 0.40 μg (range, 0.18 to 1.46; normal value, 0.06 to 0.26 μg) and the median IgG index was 1.23 μg (range, 0.45 to 2.2; normal value, <0.76). The total protein concentration was within normal range in all specimens, and the WBC count varied from 1 to 26/mm$^3$ (median, 5/mm$^3$). During IVIG treatment, the median CSF IgG concentration increased slightly (0.13 μg; range, −0.2 to 0.3), whereas it was almost unchanged during the placebo period (0.02 μg; range, −0.19 to 0.7). The difference in CSF IgG concentrations between the two treatment periods was statistically significant ($p =$

***Table 4*** *Changes in total lesion load in T2-weighted MRI (per-protocol population; n = 18)*

| | IVIG | | Placebo | | |
|---|---|---|---|---|---|
| | Start | End | Start | End | *p* Value |
| T2 lesion load (mm$^2$) | | | | | |
| *Mean ± SD* | 4,378 ± 4,528 | 4,123 ± 4,022 | 4,487 ± 4,835 | 4,301 ± 3,883 | NS* |
| Change in T2 lesion load (mm$^2$) | | | | | |
| Mean ± SD | −255 ± 1,085 | | −185 ± 1,295 | | |
| Median (range) | −108 (−3,855–1,315) | | −7 (−3,008–1,361) | | NS† |
| % change in T2 lesion load | | | | | |
| Mean ± SD | 3.4 ± 38.0 | | 33.5 ± 98.1 | | |
| Median (range) | −2.6 (−39.9–128.9) | | −0.4 (−32.6–404.2) | | $p = 0.27$† |

* Comparison of start and end of treatment periods.
† IVIG vs placebo (Wilcoxon signed-rank test for pair differences).

IVIG = intravenous immunoglobulin G; NS = not significant.

*Table 5 Acute exacerbations*

| | Intention-to-treat analysis (n = 21) | | | Per-protocol analysis (n = 18) | | |
|---|---|---|---|---|---|---|
| | IVIG | Placebo | 2*p* Value | IVIG | Placebo | 2*p* Value |
| No. of exacerbations | 11 | 19 | 0.13 | 11 | 15 | 0.33 |
| No. of severe exacerbations | 3 | 7 | 0.22* | 3 | 6 | 0.36* |
| Exacerbation-free patients | 15 | 7 | 0.02† | 12 | 6 | 0.07† |

* IVIG vs placebo (Wilcoxon signed-rank test for pair differences).
† IVIG vs placebo (McNemar test).

IVIG = intravenous immunoglobulin G.

0.0008). No significant changes were found in the IgG index or WBC count.

*Adverse events and safety parameters.* We observed an unexpectedly high number of acute and chronic adverse events. The acute side events developed during the infusion or the following day; they were transient and usually mild. The most frequently occurring acute adverse events associated with 133 IVIG infusions and 124 placebo infusion were headache (IVIG 34, placebo 8), nausea (IVIG 12, placebo 0), and urticarial rashes (IVIG 9, placebo 1). Headache was usually mild, lasting for 1 or 2 days, and was controlled by analgesics. A reduction in infusion rate of IVIG significantly decreased the occurrence of postinfusion headache and nausea. Urticaria rashes could be abolished or diminished by administration of antihistamine before the infusion.

The most serious chronic complication was seen in one patient, who developed biochemical signs of liver disease and subsequently was found to have hepatitis C (HCV RNA detected by the polymerase chain reaction). The most common major chronic side effect was severe eczema observed in 11 patients during treatment with IVIG, and this was the most common cause for withdrawal from the study. The eczematous reaction developed 2 to 4 days postinfusion after the first course of IVIG in four patients, after the second course in six patients, and after the fourth course in one patient. The eruption started in the palms of the hands in nine patients, spread to the soles of the feet and extremities in six patients, and became generalized in two, either over a period of 2 to 3 weeks or after subsequent courses of IVIG. In two patients the skin changes were confined to the face. After the first eruption, eczema resolved somewhat before the next course of IVIG in four patients, but later it did not resolve between courses. The eczema increased in severity and extension with repeated courses of IVIG in all but two patients. The maximum severity of the skin eruptions was mild in three patients, moderate in four patients, and severely incapacitating in four patients. The palmar eczematous eruption started as small papules or vesicles evolving into a scaly eruption with fissures, which in the most severe cases were hemorrhagic. On the face, extremities, and body, the appearance of the rash varied. In some patients the elements were small circular spots, in some a nummular eczema, and in others confluent but almost always scaling. Complaints of itching were common. All patients were examined by a dermatologist, who classified the eczema as a nonspecific nummular eczema or suggestive of a toxic eczema. A skin biopsy from a patient with a severe outbreak showed a nonspecific eczematous process: epidermal hyperkeratosis and parakeratosis and nonspecific dermal inflammation with perivascular infiltration by lymphocytes, plasma cells, and a few eosinophilic leukocytes. Nine patients were treated with topical steroids with moderate improvement in four. None of the patients received systemic corticosteroid treatment. In all patients, the eczema eventually resolved after discontinuation of IVIG therapy, but in some patients it persisted for several weeks after the last infusion.

Four patients withdrew from the study during the period of IVIG treatment: two because of severe eczema, one had an episode of major depression that was thought to be unrelated to the IVIG treatment, and one patient with an EDSS score of 7.0 died from a pulmonary embolism that occurred more than 2 weeks after he received an IVIG infusion as a complication to a deep venous thrombosis in the leg. Four patients left the study during the placebo treatment period: one because of severe hand eczema that developed during the preceding IVIG treatment period, one because of treatment failure after three severe relapses during the placebo treatment, one who did not want to continue the controlled trial, and one who emigrated to Singapore.

**Discussion.** Treatment with IVIG reduced the MRI activity in patients with relapsing MS. Serial MRI provided objective measurements of the thera-

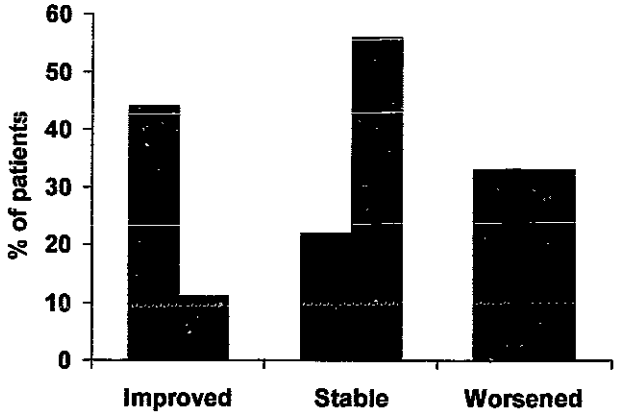


*Figure 2. Changes in disability on the Expanded Disability Status Scale during treatment with intravenous immunoglobulin G (IVIG; gray bars) and placebo (black bars).*

peutic efficacy of IVIG treatment, and the study was designed to determine a significant reduction in the number of gadolinium-enhancing lesions. Both the number of new lesions and the total number of lesions were reduced by more than 60% compared with placebo, and 22% of the patients did not exhibit any signs of MRI activity during the 6 months of IVIG treatment compared with no patients during placebo treatment. It is well known that corticosteroid treatment has a significant effect on gadolinium enhancement of acute MS lesions. However, only two patients had MRI within 4 weeks after IV methylprednisolone, and hence the MRI results may not have been affected by corticosteroids.

We also found a trend toward a reduction of acute exacerbations during IVIG treatment compared with placebo. A significantly higher proportion of patients were exacerbation free, and the number of clinical relapses were lower on IVIG than on placebo, although the difference did not reach statistical significance. However, the study was not powered to show statistical differences in any of the secondary clinical efficacy parameters.

We chose a crossover study design with frequent monitoring of gadolinium-enhancing lesions on MRI as an outcome measure because the number of patients and the duration of treatment required to demonstrate a significant treatment effect could be reduced, compared with a parallel group study with clinical efficacy parameters. We chose a washout period of 3 months based on a plasma half-life of IgG of approximately 3 weeks and on the duration of IVIG effects in other neuroimmunologic diseases. The disadvantage of the two-period crossover design is the possibility of a carryover effect in patients treated with the sequence active drug followed by placebo. In case of a prolonged carryover effect, the beneficial influence of the active drug will continue during a part of the placebo period and hence the difference between the active drug and placebo could be underestimated. In our study, we found a period effect for the sequence of IVIG treatment regarding only the number of gadolinium-enhancing lesions in the per-protocol study, showing that IVIG was better in the first treatment period than in the second treatment period. However, although we found an effect of the treatment order (period effect) for the IVIG treatment, no period effect was found regarding the placebo treatment, and hence no carryover effect was present. Another disadvantage of crossover trials is that the results are significantly weakened if a large proportion of the patients do not complete the trial. In fact, our study was hampered by an unexpectedly large number of dropouts, making only 21 of 26 patients eligible for the intention-to-treat analyses and 18 for the per-protocol analyses.

Our findings are in accordance with previous uncontrolled open-labeled studies of IVIG in MS.[15-18] The results also lend support to the conclusions of a recently published randomized placebo-controlled trial by Fazekas et al.,[19] who performed a parallel group study of 150 patients randomly assigned to treatment with IVIG 0.15 to 0.20 g/kg/month or placebo. They demonstrated a 59% reduction in the annual relapse rate during IVIG treatment compared with placebo and a significant decrease in the EDSS score in IVIG-treated patients compared with an increase in the placebo group. Unfortunately, MRIs were not obtained, and the treating physician was not blinded to the treatment allocation, which may have made it difficult to maintain blinding of all patients during a 2-year study, although the occurrence of relapses was determined by a blinded physician.[19]

In our study, we used an IVIG dose of 2 g/kg/month, which was approximately 10 times higher than that used by Fazekas et al.[19] A striking difference between the two studies was the frequency of adverse events. In the study by Fazekas et al., only three patients (4%) in the IVIG-treated group reported side effects, whereas more than 50% of the patients in our study experienced one or more adverse events from IVIG treatment. The most serious complication was the transmission of hepatitis C virus to one patient.[26] This risk has very likely been overcome by the new virus inactivation process (solvent-detergent treatment) currently used. Although recent reports indicate that adverse effects are not uncommon when IVIG is administered intravenously in high doses, no previous studies reported adverse effects in a frequency comparable with that observed in our study.[27,28] The high dose and infusion rates, 1 g/kg administered over 3 to 5 hours, resulting in very high plasma IgG concentrations were probably responsible for the high frequency of headache, nausea, and skin reactions. Headache is a well-known side effect of IVIG and directly related to the infusion rate.[27] Eczema has been described in case reports, but the pathophysiologic mechanisms for this adverse event are unknown.[27,29,30] In the present study, eczema occurred with a higher frequency and severity than hitherto reported. No other drugs were suspected to be responsible, and the high frequency and the temporal association with IVIG indicate a causal relationship. The occurrence of eczema was not batch specific; neither did it seem to be related to the solvent-detergent virus inactivation, because it developed after infusion of the old Gammagard product as well as the solvent-detergent preparation. It is not likely that Gammagard has any specific propensity for causing eczematous reactions because this drug was used in a large clinical trial in Guillain-Barré syndrome where no significant skin reactions were reported.[1] Further, previous reports of eczematous eruptions have occurred with other brands of human immunoglobulin.[27,29,30]

Could the reaction be unique for MS patients? It is possible, but IVIG has been used, although in much lower doses, in several trials in MS and no eczematous skin reactions were reported.[15-19] We suspect that the occurrence of eczema could be related to the very high plasma IgG concentrations, resulting from

high doses (1 g/kg) of IVIG infused over 3 to 5 hours, and the mechanism could be that IVIG contains substances that in very high concentrations are toxic to the skin. The frequent occurrence of eczema in our clinical trial urges us to advise caution with rapid infusion of large doses of IVIG in patients with MS.

One patient died from a pulmonary embolism originating from a femoral vein thrombosis. The patient had an EDSS of 7.0 at the start of IVIG treatment and was confined to a chair most of the day. It is well known that the use of high doses of IVIG causes a slight increase in plasma and whole blood viscosity that could favor thrombosis in patients already at risk of thromboembolic events.[27] Because the pulmonary embolism developed more than 2 weeks after he had received the last IVIG infusion, it was concluded that it was unlikely that the IVIG infusion was directly associated with the embolism. Nevertheless, it might suggest caution in using IVIG in chairbound patients who have a high risk of deep vein thrombosis.

The large number of side effects made it difficult to maintain blindness in all patients throughout the study, and this may have caused bias in the evaluation of clinical variables. Fortunately, the main efficacy parameter was the occurrence of gadolinium-enhancing lesions on MRI that could be evaluated objectively by blinded neuroradiologists.

The 60 to 69% difference in the median number of gadolinium-enhancing lesions per patient in our study was comparable with the reduction of gadolinium-enhancing lesions obtained by interferon beta. Jacobs et al.[31] found that weekly IM administration of interferon beta-1a 6 mIU produced a reduction in the number of patients with active scans from 53% at baseline to 30% after 1 and 2 years. Pozzilli et al.[32] reported a decrease in the median number of gadolinium-enhancing lesions on monthly MRI from 1.7 in a 6-month pretreatment period to 0.8 (53% reduction) during 6 months of subcutaneous administration of interferon beta-1a, 3 mIU weekly, and from 0.7 to 0.2 (71% reduction) in a group who received subcutaneous administration of interferon beta-1a, 9 mIU weekly.

*Two other placebo-controlled randomized studies* of IVIG in MS have been concluded. Achiron et al.[33] randomly assigned 40 patients with relapsing-remitting MS to treatment with IVIG at a loading dose of 2 g/kg followed by 0.4 g/kg every 2 months for 2 years or placebo. They observed a 39% reduction of the annual relapse rate during IVIG compared with placebo but no change in neurologic disability. Poehlau et al. conducted a trial in 40 patients with secondary progressive MS randomly assigned to treatment with either IVIG 20 g or placebo every 2 weeks for 1 year. They reported that more patients showed improvement and fewer patients showed worsening neurologic disability during treatment with IVIG compared with placebo. They also found a significant reduction of 50% in the relapse rate and an improvement in VEP during IVIG compared with placebo (personal communication, 1997).

The mode of action of IVIG remains unknown. It is uncertain whether the effects of IVIG are confined to the blood circulation and the immune system outside the CNS or whether sufficient amounts of IgG enters the CNS to influence the local immune response within the MS lesion.[20,34] We found a significant increase in the CSF IgG concentration during IVIG therapy compared with the pretreatment level. Although this observation does not explain the mechanism by which IVIG influences MS pathology, it suggests that measurable amounts of IgG enters the CNS during IVIG treatment or, alternatively, that IVIG might induce an alteration of the intrathecal immune response.

In recent years it has been shown in the Theilers virus mouse model of demyelination that polyclonal mouse IgG promoted CNS remyelination.[12-14] Analyses of MEPs in those patients who were stabile without relapses during the IVIG treatment period showed that 10 of 12 patients improved in the CMCI, which may be indicative of remyelination in the central motor pathways.

The results of the present study are encouraging and together with the findings of other double-blind randomized studies suggest that IVIG is of benefit in relapsing MS. Studies in different subgroups of MS patients using both clinical and MRI end points in large parallel group trials are needed. The dosage regimen used in the present study seems to be above the maximum tolerated dose. The optimum dose remains unknown.


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