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REVIEW ARTICLE

Intravenous immunoglobulin G for the treatment of relapsing–remitting multiple sclerosis: a meta-analysis

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Intravenous immunoglobulin (IVIG) has several effects on the immune system that could have a beneficial influence on disease processes in multiple sclerosis (MS). Four double-blind trials in relapsing–remitting MS have demonstrated that IVIG may reduce the relapse rate, progression and the number of gadolinium-enhancing lesions. However, these trials were smaller than the pivotal trials of interferon-β and glatiramer acetate, and therefore, we performed a meta-analysis of the four trials in order to provide an overall assessment of the benefits of IVIG in relapsing–remitting multiple sclerosis in comparison with other drugs currently available for treatment of disease activity in MS. The meta-analysis showed a significant beneficial effect on the annual relapse rate (effect size −0.5; $P = 0.00003$), on the proportion of relapse-free patients (0.29 difference; $P = 2.1 \times 10^{-8}$), change in Expanded Disability Status Scale (EDSS) score (effect size: 0.25; $P = 0.04$), and a trend towards a reduction in the proportion of patients who deteriorated ($P = 0.03$). Each single study in the meta-analysis had its weaknesses, but all studies were positive regarding their primary end-point, and the results yield concordant evidence for reduction of relapse rate and progression. The ideal dosage of IVIG for treating MS needs still to be determined. In conclusion, IVIG may be a valuable alternative for treatment of relapsing–remitting MS, but can presently not be considered as a first-line treatment. IVIG could be considered in patients who do not tolerate or are unwilling to take the approved injectable medications, but additional studies are needed to establish the role of IVIG in the management of multiple sclerosis.

Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating chronic disease of the central nervous system. According to the current hypothesis, MS is an autoimmune disease directed against multiple brain antigens with different immunological mechanisms. These include T-cell mediated brain inflammation, antibody- and complement-mediated demyelination, and primary oligodendrocyte pathology (Lucchinetti *et al*., 1996; Storch and Lassmann, 1997). Intravenous immunoglobulin G (IVIG) is an established therapy in a number of autoimmune neurological disorders and has a number of properties which may be beneficial in MS (Dalakas, 1998; Kazatchkine and Kaveri, 2001).

A number of open-labelled studies have indicated effect on MS disease activity (Sorensen, 1996) and, within the last years, four randomized, placebo-controlled trials have evaluated the effect of IVIG treatment in relapsing MS (Fazekas *et al*., 1997; Achiron *et al*., 1998; Sorensen *et al*., 1998; Lewanska *et al*., 2002). All four studies have shown effect on various outcome measures, but all studies were smaller, and, hence, the results are considered less robust than those of the pivotal trials of interferon-β and glatiramer acetate (The IFNB Multiple Sclerosis Study Group, 1993; Johnson *et al*., 1995; Jacobs *et al*., 1996; PRISMS Study Group, 1998; Comi *et al*., 2001.

We have performed a meta-analysis of the four trials in order to provide an overall assessment of the benefits of IVIG in relapsing–remitting MS in comparison with other drugs currently available for treatment of disease activity in MS.

Methods

For the meta-analysis we considered only those trials that had examined the efficacy of IVIG in relapsing–remitting MS in a randomized, placebo-controlled

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manner. As noted, we were able to identify four published studies which met these inclusion criteria (Fazekas *et al*., 1997; Achiron *et al*., 1998; Sorensen *et al*., 1998; Lewanska *et al*., 2002), and, to the best of our knowledge, represent the sum total of all such trials in this patient population. Thus, our meta-analysis was comprehensive in this regard.

For the quantitative outcomes of EDSS score and annual relapse rate, the combination of results was based on the use of the effect size, Δ/σ, where Δ is the difference in mean results for IVIG and placebo and σ is the common (population) standard deviation (SD). These quantities are estimated for each study by the difference in mean scores and the pooled estimated (sample) SD, σ. (Note that the ratio of these estimates is biased and a bias adjustment as described by Hedges and Olkin (1985) was considered in the analysis, although this had no discernable effect on the outcome. These results were pooled together using weights based on the sample sizes for each trial and study preparation using basic techniques described by Hedges and Olkin (1985). However, before pooling all of the results, a chi-square test for homogeneity was conducted [also described by Hedges and Olkin (1985)]. If this test was significant, an attempt was made to eliminate the result(s) that may have caused the heterogeneity and the remaining findings were then combined.

For the qualitative outcomes of relapse-free and deterioration rates, the basic approach as described by Ingelfinger *et al*. (1994) was employed. Here the effect size is simply the difference in proportions between the active and placebo groups. Basically, these values are weighted according to the reciprocal of the binomial variance (based on the difference in proportions). A test of homogeneity of results was also used following a simple modification of the chi-square procedure mentioned above. In addition, odds ratios were computed for each study and overall, as well as 95% confidence intervals assuming a fixed effect model and employing the Mantel–Haenszel method (Petitti, 1994). An exact test for homogeneity of the odds ratios was computed using the method of Zelen (1971). These calculations were implemented using StatXact5 (Cytel Software Corporation, Cambridge, MA, USA 2001).

Results

Patients and study design

In all 265 patients were enrolled in the four trials. All patients had definite relapsing–remitting MS except for five patients in the study by Sorensen *et al*. (1998) who had secondary progressive MS with relapses; however, these individuals were included in the analysis. Patient characteristics, IVIG dosage, and trial duration are given in Table 1. Three of the studies used a parallel group design, whereas one study was a crossover trial with two 6-month treatment periods. The trial durations in the parallel group studies were 24 months in two studies and 12 months in the other. The dosage of IVIG varied considerably, from 0.15 to 0.2 g/kg bodyweight monthly in the study by Fazekas *et al*. (1997) to 2.0 g/kg bodyweight monthly in the study by Sorensen *et al*. (1998). The three parallel-group studies used saline as placebo, whereas Sorensen *et al*. (1998) used 2% albumin as placebo.

The studies employed different primary efficacy endpoints. In the Fazekas *et al*. (1997) study, the primary outcome measures were the change in EDSS and the proportion of patients who improved, remained stable or worsened in disability, defined as an increase or decrease of at least 1.0 point in the EDSS score by the end of the study. Secondary outcome measures included the annual relapse rate and the proportion of relapse-free patients.

The study of Achiron *et al*. (1998) used the annual relapse rate as the primary efficacy endpoint. Other clinical endpoints were the proportion of exacerbation-free patients and changes in neurological disability measured on the EDSS scale. Magnetic resonance imaging (MRI) examinations were performed at baseline and after 1 and 2 years and were analysed by generating an arbitrary MRI score based on the number and diameter of the demyelinating plaques. No

Table 1 Design, patient characteristics, IVIG doses and trial duration

Study	Design	Type of MS	*n*	Age (years)	MS duration (years)	EDSS	Monthly IVIG dose	Trial duration (months)	Primary end-point
Fazekas *et al*. (1997)	PG	RR	150	37	7	3.3	0.15–0.2 g/kg	24	EDSS changes
Achiron *et al*. (1998)	PG	RR	40	35	4	2.9	0.2 g/kg	24	Relapse rate
Sorensen *et al*. (1998)	DC	RR/SP	26	35	5	3.5	2.0 g/kg	6 × 2	MRI lesions
Lewanska *et al*. (2002)	PG	RR	49	38	8.5	3.0	0.2 g/kg 0.4 g/kg	12	Relapse rate

PG, parallel groups; DC, double cross-over; RR, relapsing–remitting; SP, secondary progressive with relapse, IVIG, intravenous immunoglobulin; MS, multiple sclerosis; EDSS, Expanded Disability Status Scale.

measurements of the lesion area were performed and the study did not include MRI with gadolinium contrast.

The study of Sorensen *et al.* (1998) applied monthly gadolinium-enhanced MRI and used the total number of gadolinium-enhancing lesions and the number of new enhancing lesions as primary study endpoints. Lesion area measurements were obtained from proton density images at baseline and at the end of each of the two 6-month treatment periods. Clinical efficacy measures included relapse rate, proportion of relapse-free patients and EDSS changes from baseline to month 6.

The most recently published study by Lewanska *et al.* (2002) used the annual relapse rate and a comparison between pre-study relapse rate and relapse rate during the study period as primary clinical efficacy measures. The secondary clinical endpoints included the proportion of relapse-free patients, mean changes in the EDSS, and the proportion of patients with worsening in clinical disability by 0.5 points on the EDSS, sustained for at least 3 months. MRI endpoints included changes in lesion volume on T2-weighted images and the mean number of gadolinium-enhancing lesions on T1-weighted scans every 3 months.

Although the studies used different primary clinical endpoints, a number of major efficacy endpoints were common to all four studies and available for a meta-analysis.

Relapses

Table 2 shows the effect on the annual relapse rate. The difference in the yearly exacerbation rate expressed as an effect size (IVIG–placebo/SD) was −0.5 with a 95% confidence interval of −0.73 to −0.27. This difference is statistically significant with a two-tailed *P*-value of $P = 0.00003$. A test of heterogeneity among the studies was not significant ($P = 0.28$), justifying pooling of all four studies. The difference in the proportion of relapse-free patients was 0.29 with a 95% confidence interval of 0.18–0.39. The difference is statistically significant with a two-tailed *P*-value of 2.1×10^{-8} (Table 3). A test of heterogeneity yielded a result of $P = 0.22$. The odds-ratios for being relapse-free with 95% confidence intervals for each study and the overview result are given in Fig. 1.

Disability

All studies showed a trend towards a reduction in EDSS score during IVIG treatment and an increase in EDDS during placebo treatment when comparing baseline to the score at the final time point in the study. The decrease in EDSS score defined as an effect size (EDSS-change/SD) was −0.25 with a 95% confidence interval from −0.46 to −0.01(Table 4). The difference is statistically significant ($P = 0.042$). There was no evidence of heterogeneity among the studies ($P = 0.997$), indicating that the results were consistent over the trials considered.

Three of the four studies reported the proportion of patients who improved, and all four studies provided an analysis of the proportion of patients who deteriorated. The definition of improvement and deterioration was different between the trials. Fazekas *et al.* (1997) and Achiron *et al.* (1998) defined improvement and deterioration by a change of 1 point or more in the EDSS at the end of the study, whereas Sorensen *et al.* (1998) and Lewanska *et al.* (2002) applied changes by 0.5 points or more in the EDSS at the end of the study. The study by Sorensen *et al.* (1998) was a short time crossover trial with treatment periods of 6 months. We decided to omit this study from the analyses of the proportion of patients who improved or deteriorated, because, only few patients could be expected to show either improvement or deterioration, and such changes would primarily be related to relapses. The meta-analysis showed a

Table 2 Clinical relapse rate (mean ± SD)

Study	IVIG	Placebo	Effect size[a]	Weight[b]
Fazekas *et al.* (1997)	0.52 ± 0.87	1.26 ± 2.2	−0.44	0.51
Achiron *et al.* (1998)	0.59 ± 0.67	1.61 ± 0.98	−1.22	0.12
Sorensen *et al.* (1998)[c]	1.04 ± 1.74	1.80 ± 3.14	−0.30	0.15
Lewanska *et al.* (2002)				
0.2 g/kg	0.88 ± 1.26	1.24 ± 0.75	−0.35	0.12
0.4 g/kg	0.87 ± 0.99	1.24 ± 0.75	−0.43	0.11
Overall effect size (95% confidence interval):			−0.5 (−0.73 to − 0.27) $P = 0.00003$	

IVIG, intravenous immunoglobulin; SD, standard deviation.

[a]Effect size: IVIG – placebo/SD; [b]proportion of the reciprocal of the total variation attributable to the given study; [c] extrapolated from 6 month data.

Table 3 Proportion of relapse-free patients

Study	IVIG	Placebo	Effect size[a]	Weight
Fazekas *et al.* (1997)	0.53	0.36	0.17	0.23
Achiron *et al.* (1998)	0.35	0	0.35	0.40
Sorensen *et al.* (1998)	0.71	0.33	0.38	0.13
Lewanska *et al.* (2002)				
0.2 g/kg	0.47	0.11	0.36	0.13
0.4 g/kg	0.50	0.11	0.39	0.11
Overall effect size (95% confidence interval):			0.29 (0.18–0.39) $P = 2.1 \times 10^{-8}$	

[a]Effect size: difference in proportion: IVIG, intravenous immunoglobulin – placebo.

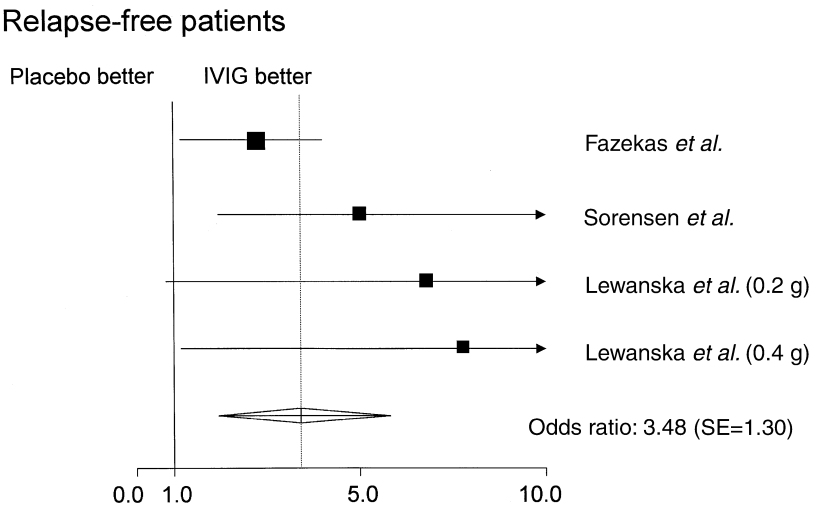

Figure 1 Odds ratios (IVIG:placebo) for staying relapse-free. Trial results and 95% confidence intervals are shown –■–. Area of ■ is proportional to amount of information contributed. ◇ = overview results and 95% confidence limits.

Table 4 Changes in EDSS[a] (Mean ± SD)

Study	IVIG	Placebo	Effect size[b]	Weight[c]
Fazekas *et al.* (1997)	−0.24 ± 1.50	0.12 ± 1.80	−0.22	0.50
Achiron *et al.* (1998)	−0.3 ± 1.46	0.15 ± 1.07	−0.35	0.14
Sorensen *et al.* (1998)	0.0 ± 1.0	0.2 ± 0.6	−0.24	0.14
Lewanska *et al.* (2002)				
0.2 g/kg	−0.07 ± 2.13	0.29 ± 1.62	−0.19	0.11
0.4 g/kg	−0.03 ± 1.39	0.29 ± 1.62	−0.21	0.11
Overall effect size (95% confidence interval)			−0.24 (−0.46 to −0.01) $P = 0.042$	

IVIG, Intravenous immunoglobulin; EDSS, Expanded Disability Status Scale.

[a]Changes in EDSS from baseline to end of study; [b]Effect size: IVIG – placebo/SD; [c]Fraction of the reciprocal of total variation attributable to the given study.

significant difference in the proportion of patients who improved on IVIG compared with placebo treatment (Table 5). A test for heterogeneity across the studies was significant for this variable ($P = 0.0003$).

The proportion of patients who deteriorated did not show significant differences in any single study, but the majority of studies reported a trend towards a beneficial effect of IVIG. The meta-analysis showed a strong trend in the proportion that deteriorated between placebo and IVIG-treated patients ($P = 0.03$; Table 5). However, there was a large degree of heterogeneity in these results ($P = 0.0001$). On the other hand, the odds ratios were not significantly different ($P = 0.28$). Figure 2 shows the odds-ratios for progression in EDSS for each study and the overall result with 95% confidence intervals.

Table 5 Proportion of patients with improvement or deterioration in EDSS

Study	IVIG	Placebo	Effect size[a]	Weight
Improved[b]				
Fazekas *et al.* (1997)	0.31	0.14	0.17	0.75
Achiron *et al.* (1998)	0.24	0.11	0.13	0.25
Overall difference (95% confidence interval)			0.16 (0.04–0.28) $P = 0.006$	
Deteriorated[b]				
Fazekas *et al.* (1997)	0.16	0.23	0.07	0.59
Achiron *et al.* (1998)	0.14	0.17	0.03	0.19
Lewanska *et al.* (2002)				
0.2 g/kg	0.24	0.47	0.23	0.10
0.4 g/kg	0.07	0.47	0.40	0.13
Overall difference (95% confidence interval)			0.11 (0.009–0.21) $P = 0.03$	

[a]Effect size: Difference in proportion improved: IVIG – placebo, and differences in proportion deteriorated: placebo – IVIG; [b]Changes by ≥1.0 points in EDSS in the studies by Fazekas *et al.* (1997) and Achiron *et al.* (1998) and by ≥0.5 points in EDSS in the study by Lewanska *et al.* (2002).

IVIG, Intravenous immunoglobulin; EDSS, Expanded Disability Status Scale.

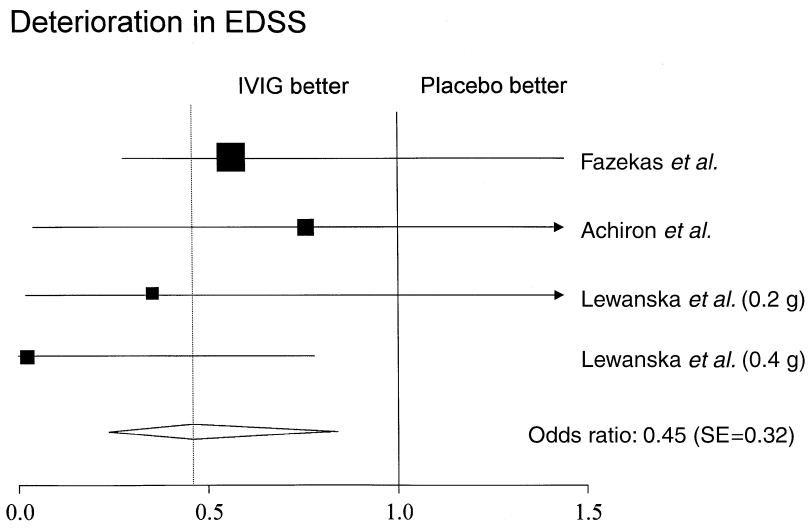

Figure 2 Odds ratios (IVIG:placebo) for deterioration in EDSS. Trial results and 95% confidence intervals are shown –■–. Area of ■ is proportional to amount of information contributed. ◇ = overview results and 95% confidence limits.

Magnetic resonance imaging

The results for MRI were not consistently reported between the three studies that used this as an endpoint. Therefore, these findings could not be combined.

Discussion

The present overview confirms that IVIG has a beneficial effect on relapses and disability changes in patients with relapsing–remitting MS. Despite the differences between the four trials included in the meta-analysis, the results seem remarkably consistent. All studies were positive regarding the primary efficacy end-point, and the results yield concordant evidence for different type of end-points, i.e. relapses and progression.

The studies, however, had different design, duration and end-points, and each single study had its weaknesses. The study of Fazekas *et al.* (1997) had, as primary outcome measures, the between-group differences at the end of the study in the mean change of the EDSS score and in the proportion of patient in each group that improved, remained stable or worsened in disability (defined as an increase or a decrease of at least 1 point in EDSS). No confirmation of the changes in EDSS was required, and hence worsening in disability at the end of the study included relapse-related deterioration. The substantial difference in the annual relapse rate of 59% between IVIG and placebo-treated patients was a result of a strong reduction in the annual relapse rate on therapy, compared with baseline in the IVIG group. Contrary to the results of most placebo-controlled trials in MS, this study showed no reduction in the annual relapse rate in the placebo group as a result of an expected regression to the mean, at least when analysing according to the principle of the last observation carried

forward. This would tend to overestimate the effect of IVIG compared with other therapies. The problem of unblinding patients, because of use of saline as placebo, has been raised. Unfortunately, no MRI investigations were performed in the study to support the clinical results.

The study by Achiron *et al.* (1998) showed a very strong reduction in the annual relapse rate in patients treated with IVIG, but like in the study by Fazekas *et al.* (1997) placebo-treated patients did not show any reduction in the annual relapse rate over time. In fact there was a slight trend towards an increase in the relapse rate during the first year on placebo treatment. They found a trend towards reduction in neurological disability in the IVIG group compared with a minor increase in the placebo group, but the difference was not statistically significant. There was significant difference in the distribution of neurological disability comparing the proportion of patients within each group who improved, remained stable or worsened, but the changes in EDSS were not confirmed and included relapse-related declines. Also, the small number of patients in the study and the lack of clearly interpretable MRI data must be considered as a limiting factor in this study.

The study by Sorensen *et al.* (1998) was different from the other studies in using a crossover design. Results of a crossover trial cannot readily be used for comparison with parallel group studies. For simplicity, the results from the two study-arms were evaluated as independent in order to obtain comparability within the three studies using a parallel group design. This could have introduced a methodological error in favour of a beneficial effect of IVIG. Many dropouts, primarily because of adverse effects of IVIG, hampered the study, and the large number of dropouts weakened the results when the two treatment periods are considered as independent. Further, the study was not powered to show changes in clinical efficacy measures, and, although the study was conducted as a double-blind trial, the same physician was treating the patients and evaluating the clinical end-points. The treatment periods were only 6 months and therefore we decided, as mentioned before, to leave out this trial from the analyses of patients who improved or deteriorated in EDSS scores.

Lewanska *et al.* (2002) performed a three-arm study comparing two different doses of IVIG with placebo; however, the number of patients in each treatment arm was very low, and the study period only 12 months, which makes it difficult to interpret the results. Changes in EDSS were defined as increases or decreases by 0.5 points, and in the lower parts of the EDSS scale such changes would include random variations. The MRI analyses of gadolinium-enhancing lesions and new T_2-lesions based on examinations every 3 months, showed considerable fluctuations making it difficult to evaluate the true magnitude of reduction of disease activity.

Some other limitations of this meta-analysis also need to be considered. It is often pointed out that meta-analyses run a risk of overestimating the effect of a new therapy because of a publication bias against negative trials. On the other hand, almost all previous open-labelled trials in relapsing–remitting MS have also indicated a beneficial effect and, to our knowledge, no negative placebo-controlled trial has ever been announced or reported; therefore, this meta-analysis was at least complete and comprehensive.

The different doses of IVIG used in the trials, of which only one included a comparison of two different doses, makes it impossible to define the optimum dose of IVIG. It can, however, be concluded that the use of very high doses of IVIG in patients with MS is likely to be associated with frequent and often severe adverse effects, whereas low doses are well tolerated.

These uncertainties of dosage further contribute to the difficulties in comparing the effect of IVIG with the effect of the approved therapies, interferon-β and glatiramer acetate. The reduction in relapse rate in the IVIG studies appears to be greater than that seen in studies of interferon-β and glatiramer acetate. However, the smaller sample size of the IVIG studies and the lack of a reduction of relapse rate in the placebo group have to be taken into consideration. Regarding the effect on disease progression and on MRI variables, data from the pivotal studies of interferon-β and glatiramer acetate clearly are more robust and convincing (The IFNB Multiple Sclerosis Study Group, 1993; Johnson *et al.*, 1995; Jacobs *et al.*, 1996; PRISMS Study Group, 1998; Comi *et al.*, 2001).

Recently, the results of a large placebo-controlled trial in secondary progressive MS have been presented, but not yet been published (Hommes *et al.*, 2002). Although, it has been shown that this phase of the disease is less amenable to therapy, it is worrying that IVIG did not show a beneficial effect on the relapse rate or MRI results thought to reflect disease activity.

In conclusion, the results of the meta-analysis indicate that IVIG is a valuable alternative to the established therapies in relapsing–remitting MS. As outlined, a number of questions regarding the efficacy of IVIG are still unanswered and therefore IVIG can presently not be regarded as a first line therapy in relapsing–remitting MS. IVIG has the advantage of requiring only monthly infusions, and doses of 0.2–0.4 g/kg imply only mild and infrequent side-effects. It is a major problem however, that the optimum dose is still unknown. This has to be established in a sufficiently large dose-finding study in relapsing–remitting MS

patients including clinical as well as MRI end-points, and such a study is in preparation. Until the results of this study are known, IVIG is only a second-line therapy that can be used in patients, who are unwilling to perform frequent subcutaneous or intramuscular injections, who do not tolerate or have contraindications to the approved therapies, and IVIG could be considered in patients who do not seem to benefit from one of the established therapies.

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