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ORIGINAL ARTICLES

The Canadian cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis

THE CANADIAN COOPERATIVE MULTIPLE SCLEROSIS STUDY GROUP*

To find out whether non-specific immunosuppression is beneficial in multiple sclerosis (MS) a randomised, placebo-controlled, single-masked trial was carried out in nine university centres. 168 patients with clinically or laboratory-supported definite MS in progressive phase (deterioration by at least 1·0 on the expanded disability status scale [EDSS] in the previous year) were randomised to receive intravenous cyclophosphamide and oral prednisone (n=55); daily oral cyclophosphamide, alternate day prednisone (22 weeks), and weekly plasma exchange (20 weeks) (n=57); or placebo medications and sham plasma exchange (n=56). All patients were followed for at least 12 months (mean 30·4 months) by a monitoring neurologist, who was aware of treatment allocation, and an evaluating neurologist, who was not. The primary analysis was a comparison of rates of treatment failure (worsening of evaluating neurologist's assessment of EDSS by 1·0 or more on two consecutive 6-monthly assessments). There were no significant differences among the groups in this primary analysis (19 [35%] treatment failures with cyclophosphamide; 18 [32%] with plasma exchange; 16 [29%] with placebo). Nor were there any differences in the proportions improved, stabilised, or worsened at each 6 month assessment or in the mean change in the EDSS at the final assessment (0·81 cyclophosphamide; 0·69 plasma exchange; 0·69 placebo). A slight trend favouring the plasma exchange group at 12–24 months of follow-up was not sustained at the final assessment. This study fails to confirm previous reports that immunosuppressive treatments result in stabilisation or improvement in progressive MS.

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Introduction

Progress towards an effective treatment for multiple sclerosis (MS) has been slow. Although it is widely believed that the pathological changes of inflammation, demyelination, and gliosis result from a disturbance of the immune response[1] in genetically susceptible individuals,[2] the aetiology and pathogenesis of MS remain imperfectly

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understood. It is difficult to predict either the occurrence or the rapidity of progression.[3] Clinical methods of determining disease activity, progression, and response to treatment have been imprecise, although advances in magnetic resonance imaging may provide a means to measure these variables objectively.

Therapeutic efforts have concentrated on treatments that suppress the immune response non-specifically. Although no such approach has achieved sustained improvement or stabilisation in progressive MS patients, modest benefits have been claimed with cyclophosphamide,[4-10] plasma exchange,[7] total lymphoid irradiation,[11] cyclosporin,[12,13] and azathioprine.[14-17]

In response to two promising reports on cyclophosphamide[6] and plasma exchange,[7] physicians at nine Canadian MS clinics and members of the Canadian Apheresis Study Group joined together for a study to determine whether either or these approaches to non-specific immunosuppression could benefit patients with progressive MS.

Patients and methods

The trial design was approved by the institutional review committees at each of the nine university centres. Enrolment took place from November, 1985, to December, 1988. All patients were followed until December, 1989.

The inclusion criteria were clinically definite[18] or laboratory supported[19] definite MS judged to be in a progressive phase (evidence of deterioration of at least 1·0 point on the expanded disability status scale [EDSS][20] over the preceding 12 months); an EDSS at entry of 4·0–6·5; and age at least 15 years. Both patients with chronic progressive (progressive from onset without relapses) and relapsing progressive MS (with occasional relapses from which the patient did not recover) were eligible for randomisation to cyclophosphamide, plasma exchange, or placebo treatment (table I). Exclusion criteria were previous treatment with cyclophosphamide, cyclosporin, antilymphocyte globulin, or interferon; treatment with azathioprine or plasma exchange in the preceding year or corticosteroids in the preceding month; illnesses which might be adversely affected by any of the experimental treatments (unstable cardiovascular, liver, renal, or bone marrow disorders, autoimmune illnesses, previous malignant disorder, uncontrolled infection, or decubitus ulcers); substantial cognitive impairment; and unwillingness to use contraception throughout the trial and 2 years afterwards. We also excluded patients for whom plasma exchange personnel thought that weekly venous access would be difficult. Two superficial arm veins were required concurrently for plasma exchange.[21] Access by way of subclavian, internal jugular, or femoral veins was not permitted; nor was the use of any form of fistula, arterial-venous shunt, venous cutdown, or arterial catheter. These access sites and interventions would have been unjustified in the event of allocation to sham plasma exchange.

The trial design was reviewed with the eligible patients and family members who were given a letter of explanation and consent form. An exclusion form was completed on all patients who satisfied the inclusion criteria but either did not enter because of exclusion factors or who were eligible but refused randomisation.[22] The latter were not permitted off-protocol treatment with the investigational agents.

Randomisation was done on a day when it was possible to proceed directly with treatment. A randomisation sequence was generated separately for each centre. Patients were stratified by centre and EDSS score (below 6·0 or 6·0 and above).

Patients assigned to the cyclophosphamide group were admitted to hospital and given 1 g cyclophosphamide intravenously on alternate days. Treatment was stopped when the white blood cell count fell below $4·5 \times 10^9$/l, since we knew this would result in a nadir white blood cell count of $1·0–2·0 \times 10^9$/l, or when the patient had received 9 g cyclophosphamide. Patients received 40 mg prednisone orally for 10 days; the dose was reduced by 10 mg on alternate days and prednisone discontinued on day 16. To reduce the risk of haemorrhagic cystitis, all patients were kept well hydrated; they were catheterised and the bladder was continually irrigated (3 ml neosporin per 3 litres normal saline). Daily urinalysis was done and cyclophosphamide was discontinued if haematuria (more than 200 red blood cells per high power field) occurred. Drug-induced nausea was reduced by administration of cyclophosphamide in the evening, restriction of fluid intake, and use of antiemetics. Complete blood counts were done daily. The white blood count reached the nadir 5–7 days after the last dose of cyclophosphamide and began to recover 7 days later. Patients were nursed in isolation if the white cell count fell below $1·0 \times 10^9$/l and were discharged from hospital when it rose above $2·5 \times 10^9$/l.

TABLE I—PATIENT CHARACTERISTICS ON ENTRY TO TRIAL

—	Mean (SD)* or no (%) of group		
	Cyclophosphamide (n=55)	Plasma exchange (n=57)	Placebo (n=56)
*Age at onset (yr)**	31·9 (10·3)	29·9 (7·9)	32·1 (9·7)
*Duration of MS (yr)**	9·2 (6·4)	9·4 (5·4)	10·4 (6·7)
Female	37 (67%)	33 (58%)	32 (57%)
Class of MS			
Clinically definite	45 (82%)	50 (88%)	54 (96%)
Laboratory supported definite	10 (18%)	7 (12%)	2 (4%)
Level of MS			
Relapsing-progressive	22 (40%)	31 (54%)	28 (50%)
Chronic-progressive	33 (60%)	26 (46%)	27 (48%)
Increase in EDSS in previous year			
≤1·5	33 (60%)	42 (74%)	34 (61%)
>1·5	22 (40%)	15 (26%)	22 (39%)
*EDSS score**	5·79 (0·61)	5·66 (0·72)	5·79 (0·64)

Patients in the plasma exchange group received cyclophosphamide by mouth (1·5–2·0 mg/kg daily) for 22 weeks and alternate day oral prednisone (20 mg every other day tapered over 22 weeks). Plasma exchange of one plasma volume (40 ml/kg) was done weekly for 20 weeks with either intermittent (5 centres) or continuous (4 centres) flow-type centrifuges. 5% serum albumin was used as the replacement fluid. Urinalysis and complete blood counts were done weekly. The dose of cyclophosphamide was adjusted weekly to achieve a target white blood count of $4·0–5·0 \times 10^9$/l.

Placebo group patients were given cyclophosphamide placebo by mouth daily and prednisone placebo every alternate day for 22 weeks. Sham plasma exchange of one plasma volume was done weekly. These patients received their own plasma as replacement fluid. In both the plasma exchange and placebo groups, the apparatus and replacement fluids were shielded from the patient's view by a curtain. Adjustments were made in the dose of cyclophosphamide placebo to mimic the dose adjustments in the plasma exchange group.

Each patient was followed by both a monitoring neurologist who was aware of treatment allocation and an evaluating neurologist who was not. The monitoring neurologist supervised the experimental treatments. At entry and every 6 months, patients were examined consecutively by both neurologists. Typically they observed the patient's gait simultaneously but were instructed not to discuss their findings nor consult their previous records. Several steps were taken to ensure blinding of the evaluating neurologist. He or she was not involved with the patient's ongoing care, since most evaluating neurologists did not work in the hospital where the inpatient and outpatient treatments were given, and he or she avoided asking questions which would be informative about the treatment. At the 6 month assessment, all patients wore scalp coverings and gauze bandages around the antecubital fossae since the drug-induced alopecia and plasma-exchange-induced antecubital bruising would have indicated the treatment. Patients with exacerbations or progression were seen by the monitoring neurologist who was permitted to prescribe corticotropin or corticosteroids (prednisone, methylprednisolone). The central coordinating centre (London,

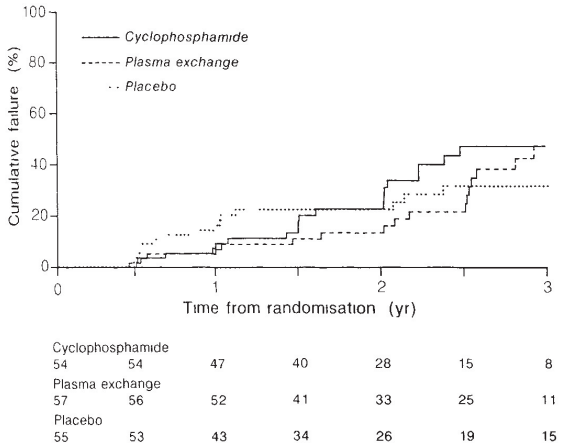

Fig 1—Time to treatment failure.

Ontario) was notified of all such cointerventions. At the end of the observation period, the patients were examined twice within 8 weeks by both the evaluating and the monitoring neurologist (final assessment and confirmatory examination).

The external safety monitoring committee monitored the progress of the trial every 6 months (severe adverse experiences, deaths, clinical status).

At the start of the trial we decided that the primary analysis would involve a comparison over time of the cumulative treatment failure rates (by means of Breslow's test[23]) in each of the three treatment groups by the techniques of survival analysis.[24] A treatment failure was defined as a worsening of the evaluating neurologist's score by 1·0 points or more (2 step change) on the EDSS on two consecutive examinations separated by at least 6 months. The first of these two examinations was taken as the time of the treatment failure. All randomised patients contributed to the survival curve until the point of treatment failure, death, or end of follow-up. Subjects who did not complete the allocated treatment were followed and their outcome was assigned to the group to which they were randomised (intention to treat analysis). All patients were followed and assessments continued until the end of the trial whether or not they met the definition of clinical failure. The sample size was calculated to detect a 30% difference in failure rate between one of the active treatments and the control group at an alpha of 0·05 (two-tailed) and a power of 90%. Secondary analyses involved the numbers of patients improved (reduction of EDSS of 1·0 or more), stabilised (change of 0·5 EDSS points or less), or worsened (increase of EDSS of 1·0 or more), the mean and median changes in the EDSS, the number of patients requiring cointervention, and the time to cointervention with cortocosteriods or corticotropin. The evaluating neurologist's judgment was used for all but nine outcome assessments. 6 patients could not return to their participating centre for the final examination. Their EDSS and functional systems (FS) scores were calculated from information supplied by their treating physicians. 3 other patients were only seen by the monitoring neurologist at the final assessment.

TABLE II—PROPORTION OF PATIENTS IMPROVED, STABLE, OR WORSE ON EDSS AT EACH ASSESSMENT*

	No (%)			Two-tailed p value	
—	Cyclophosphamide (C)	Plasma exchange (PE)	Placebo (P)	C *vs* P	PE *vs* P
6 mo	n=54	n=57	n=54		
Improved	5 *(9%)*	8 *(14%)*	3 *(6%)*		
Stable	46 *(85%)*	43 *(75%)*	42 *(78%)*	0·159	0·246
Worse	3 *(6%)*	6 *(11%)*	9 *(17%)*		
12 mo	n=48	n=48	n=48		
Improved	3 *(6%)*	4 *(8%)*	1 *(2%)*		
Stable	38 *(79%)*	39 *(81%)*	35 *(73%)*	0·295	0·086
Worse	7 *(15%)*	5 *(10%)*	12 *(25%)*		
18 mo	n=39	n=36	n=33		
Improved	2 *(5%)*	4 *(11%)*	0		
Stable	26 *(67%)*	25 *(69%)*	23 *(70%)*	0·418	0·106
Worse	11 *(28%)*	7 *(19%)*	10 *(30%)*		
24 mo	n=31	n=31	n=30		
Improved	2 *(6%)*	1 *(3%)*	0		
Stable	13 *(42%)*	25 *(81%)*	20 *(67%)*	0·088	0·201
Worse	16 *(52%)*	5 *(16%)*	10 *(33%)*		
30 mo	n=24	n=22	n=20		
Improved	0	1 *(5%)*	0		
Stable	10 *(42%)*	11 *(50%)*	13 *(65%)*	0·304	0·448
Worse	14 *(58%)*	10 *(46%)*	7 *(35%)*		
Final	n=54	n=57	n=54		
Improved	2 *(4%)*	1 *(2%)*	1 *(2%)*		
Stable	24 *(44%)*	34 *(59%)*	32 *(59%)*	0·290	0·999
Worse	28 *(52%)*	22 *(39%)*	21 *(39%)*		

*Evaluating neurologist's assessment improved = ⩾1 0 fall; stable = ⩽0 5 change; worsened = ⩾1 0 rise

Results

168 patients entered the study. The three treatment groups were well matched for age, marital status, comorbidity, duration of disease, and EDSS scores at entry (table I). All patients were followed until death or the end of the study period.

In the primary analysis there were no statistically important differences in the cumulative proportion of treatment failures over time among the treatment groups (cyclophosphamide 19 [35%]; plasma exchange 18 [32%]; placebo 16 [29%]). Although treatment failure tended to occur earlier in the placebo group, this difference was not significant (mean time to failure 24·8 [SD 7·6] mo cyclophosphamide; 29·3 [10·9] mo plasma exchange; 20·6 [9·5] mo placebo; fig 1). Neither active treatment significantly prolonged the time to treatment failure ($p=0·78$ for cyclophosphamide, $p=0·26$ for plasma exchange, compared with placebo; fig 1).

The secondary analyses of efficacy (tables II and III) included all assessments irrespective of clinical failure status. The reducing numbers at each time point are due to variable amounts of follow-up because of sequential intake spread over the 36 month enrolment period. Both tables show that the active treatment groups did slightly better than the placebo group early in the follow-up period. The small observed advantage of plasma exchange was lost after about 2 years; for cyclophosphamide the gain persisted for only 1 year, after which cyclophosphamide-treated patients fared somewhat less well than the control group. None of these differences in EDSS between the control group and either active treatment group was clinically important or statistically significant after allowance for multiple comparisons over time points.

Very few patients showed improvement in their condition after treatment in this trial (table II). Of the 16 patients

TABLE III—CHANGES IN EDSS AT EACH ASSESSMENT

	Cyclophosphamide		Plasma exchange		Placebo	
—	Mean (SEM) change	n	Mean (SEM) change	n	Mean (SEM) change	n
Baseline	*5·79 (0·08)*	55	*5·60 (0·10)*	57	*5·79 (0·09)*	56
6 mo	0·06 (0 07)	54	0·04 (0·11)	57	0·19 (0·08)	54
12 mo	0·18 (0·09)	48	0·14 (0·10)	48	0·39 (0 09)	48
18 mo	0·36 (0·11)	39	0·14 (0·18)	36	0 55 (0·12)	33
24 mo	0·81 (0·17)	31	0 29 (0·15)	31	0·67 (0·10)	30
30 mo	0·98 (0 18)	24	0·52 (0·22)	22	0·68 (0·12)	20
Final	0·81 (0·14)	54	0 69 (0 11)	57	0·69 (0·10)	54

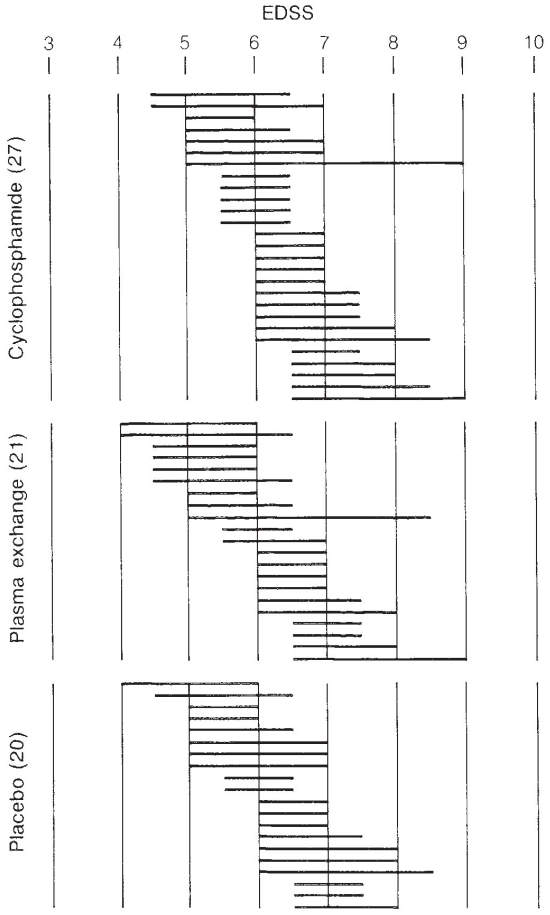

Fig 2—Extent of deterioration in EDSS.

Every patient whose EDSS increased by ≥1·0 (evaluating neurologist's assessment) at any time during trial is represented by a line connecting the EDSS score at entry with the highest (worst) EDSS score recorded during the trial. Numbers in parentheses = numbers in each group who showed an increase of at least 1 0 on the EDSS.

judged to have improved at the 6 month assessment, all but 4 improved by only 1 EDSS point, the minimum needed for classification as improved. By 12 months only 8 patients met the criteria for improvement, 5 by the 1 point minimum. The degree of clinical change in those patients judged as having deteriorated was similar in all treatment groups (fig 2).

The analysis of cointerventions by the monitoring neurologists suggested that steroids were used earlier and more often in the placebo group than in either of the two active treatment groups (table IV).

2 patients died. 6 months after randomisation 1 apparently stable cyclophosphamide-treated patient (EDSS 6·0) died within 12 h of the development of symptoms of acute bronchopneumonia. The other death occurred 33 months after randomisation in a placebo-treated patient with advanced liver disease. Two cyclophosphamide-treated patients had haemorrhagic cystitis, and 3 became septic during their hospital stays. 1 patient in the plasma exchange group was treated for vascular collapse during the 3rd month of plasma exchange and hypertension developed in 1 at 24 months. Diabetes developed in 1 patient in each of the active treatment groups and herpes zoster infection occurred in 1 patient in each of the active groups. 1 non-fatal

TABLE IV—USE OF COINTERVENTION* BEFORE CLINICAL FAILURE

	Cyclophos-phamide	Plasma exchange	Placebo
Proportion of patients receiving at least one cointervention	14/55 (25%)	8/57 (14%)	21/56 (39%)
Mean time to first cointervention (mo)	12·6	15·0	10 6
Mean no of cointerventions	1 9	1 6	2 1

*Corticotropin or corticosteroids

pulmonary embolism was diagnosed in a cyclophosphamide-treated patient. Depression requiring psychiatric treatment developed in 3 plasma exchange patients, and angina developed in 1 patient in each of the cyclophosphamide and placebo groups. Severe alopecia occurred in all the cyclophosphamide-treated patients who received more than 2 g intravenous cyclophosphamide and in 51% of the plasma exchange group (compared with 16% of placebo patients). Amenorrhoea was reported in 42% of women in the cyclophosphamide group (permanent in 24%), 77% in the plasma exchange group (permanent in 54%), and 11% in the placebo group (permanent in 7%). More than 85% of patients in all three groups took more than 80% of their medications (pill count), and 90% of patients in the plasma exchange and placebo groups completed at least 90% of the planned plasma exchange treatments. 44 of 55 cyclophosphamide-treated patients achieved a target white blood count of less than $2{\cdot}0 \times 10^9$/l.

The degree of physician and patient masking was determined at the final assessment. The evaluating neurologist was able to identify the treatment assignment in only 5% of cases. 68% of plasma-exchange-treated patients and 49% of placebo-treated patients accurately identified the treatment they received.

Discussion

The primary analysis showed no clinically or statistically important difference between either of the active treatments and placebo treatment. The slight trend in EDSS favouring the two active regimens at the 6 month and 12 month assessments must be balanced against the inconvenience, costs, and potential for serious adverse effects with these treatments and by a similar apparent net worsening in the cyclophosphamide group (compared with the placebo group) at 24 months, 30 months, and the final follow-up assessment. The EDSS is an inherently ordinal scale and unit changes may not be of equal importance over its whole range. It may therefore be inappropriate to analyse changes in the EDSS by parametric tests of significance,[25] although such tests have been used in other studies of MS.[26] The average difference in EDSS between the two active regimens and the placebo group at 6 months and 12 months (0·25 EDSS points or less) is half the smallest increment that the EDSS recognises (0·5 points). By any standard, changes of this size must be of limited clinical importance. Because of the limitations of the trial design, we cannot tell whether this short-lived apparent minor benefit was from one of the components of the active treatment protocols, a combination of these components, or a brief "placebo" response in the patients who became aware of their treatment (all of the cyclophosphamide group and 68% of the plasma exchange group). The extent of deterioration in the patients whose EDSS worsened by at least 1·0 points at

any time after randomisation was similar for all three treatment groups (fig 2).

Was any trend seen? At the 12, 18, and 24 month assessments, the proportion of patients stabilised or improved was greater in the plasma exchange group than in the other groups. The difference in the mean EDSS between the plasma exchange and placebo groups was always less than 0·5 EDSS points, however, and the trend was no longer evident at the final follow-up. In Khatri and colleagues' study,[7] 11 of 26 patients treated by plasma exchange still had improved by 1·0 or more EDSS points 11 months after the start of treatment, whereas only 4 of our 48 plasma exchange patients had improved (all by 1·0 EDSS points). Although plasma exchange is generally well tolerated,[27] 90% of our patients had some adverse effect[21] and the procedural expense must be balanced by a meaningful clinical response. It remains possible that a more aggressive or longer course of cyclophosphamide, prednisone, and plasma exchange could produce a clinically and statistically significant benefit.

Because of the theoretical risk that cyclophosphamide could potentiate the immune response[28] and thereby worsen the course of MS, the drug's known serious toxic effects,[29] and the negative results of the only previously masked, placebo-controlled study,[30] we opted for a two-tailed analysis of the data (table II). More patients were stable or improved in the first year after intravenous cyclophosphamide than placebo but this difference was not significant (table II). At all subsequent assessments, the number of patients judged to be worse was consistently greatest in the cyclophosphamide group. Patients in that group were certain they had been assigned an active treatment (single masked). Furthermore, the placebo patients did not receive prednisone. Despite these two factors, which might be expected to bias the results in favour of the cyclophosphamide group, treatment did not offer a significant advantage over placebo.

There were more cointerventions with corticotropin and steroids in placebo-treated patients. In addition, the mean time to cointervention and the mean number of cointerventions per patient suggested an advantage for the active treatments. The decision to use steroids was made by the unmasked monitoring neurologist, however. We believe that his or her knowledge of the treatment assignment may have introduced bias into the decision to intervene. It is conceivable that the monitoring neurologist might have been more inclined to use steroids earlier and more frequently in placebo-treated patients than in actively treated patients with similar degrees of deterioration. The primary analysis suggests that the combination of sham plasma exchange, placebo drugs, and the occasional use of corticotropin or steroids as needed, is as effective as the experimental treatment regimens.

Most patients in all three groups did much better in the year after entry to the trial than they had immediately before (the EDSS had fallen by 1·0 point in the preceding year). This finding clearly shows that patients cannot be used as their own controls in MS clinical trials.

Why did the study fail to confirm a benefit with immunosuppressive treatments? Although significant improvement was rare in this study, the proportion of patients stable or improved 12 months after each of the active treatments was comparable or superior to previous series[6,7,9,10] (table II). This comparability suggests that the minor differences in the active treatment protocols tested in this study did not account for the disappointing results.

Of greater importance was the difference in the behaviour of the comparison group. In Hauser and colleagues' study,[6] only 4 (20%) corticotropin-treated patients (controls) were stable or improved at 12 months compared with 36 (75%) of our placebo-treated patients and their respective mean changes (worsening) on the disability status scale (DSS) were 0·70 (0·03) and 0·39 (0·09) at 12 months. The other favourable study[7] had no untreated controls. The 75% "apparent" stabilisation rate at 1 year in our placebo group is similar to that found in natural history studies[31] and treatment trials.[17,32] Indeed, our placebo-treated patients were just as likely, if not more so, to be stable at 12 months as patients in series treated with cyclophosphamide,[6] plasma exchange,[7] and courses of cyclophosphamide with "boosters".[9,10] This remarkable "response rate" has been seen in compliant placebo-treated patients in other settings.[33] It is not clear why the corticotropin-treated patients in Hauser et al's study[6] did so much more poorly than would be expected from our knowledge of the natural history of progressive MS. Perhaps awareness of corticotropin treatment, which many might have received previously with little or no sustained benefit, had a negative effect on their disease course. If that control group had not done so poorly, that study[7] would also have yielded negative results.

Our entry criteria were more demanding than those used in the previous studies.[6,7] We aimed to minimise the numbers of patients who stabilised spontaneously during the observation period. These strict entry requirements severely restricted the number of patients eligible for randomisation and forced us to extend our enrolment period, despite our large MS clinic population (more than 7000 patients).

The degree of inter-observer variability in the use of the EDSS and FS[34] and differences in the time spent at each level of the DSS[35] suggest that the outcome measures commonly used to estimate treatment effects (eg, disability scales, time to cointervention, time to being wheelchair bound) may not be sufficiently precise to detect small but clinically relevant slowing of disease progression. More sensitive clinical and imaging indices might have shown a difference with the active protocols tested in this study. Reliable, valid, reproducible, and clinically relevant measures of treatment effect will be needed to identify when experimental treatments have changed the natural history of active, progressive MS. From our study we cannot recommend that either of the active treatments tested in this trial should be offered to patients with MS. The slight confirmed clinical worsening during this trial in the control group underscores the requirement that experimental MS treatments must be compared with a convincing placebo treatment.

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REFERENCES

1. Rationale for immunomodulating therapies of multiple sclerosis. *Neurology* 1988; **38** (suppl 2): 1–89.
2. Ebers GC, Bulman DE, Sadovnick AD, et al. A population-based study of multiple sclerosis in twins. *N Engl J Med* 1986; **315:** 1638–42.
3. Matthews WB, Acheson ED, Batchelor JR, Weller RO. McAlpine's multiple sclerosis. Edinburgh: Churchill Livingstone, 1985.
4. Gonsette RE, Demonty L, Delmotte P. Intensive immunosuppression with cyclophosphamide in multiple sclerosis: a follow-up of 110 patients for two to six years. *J Neurol* 1977; **214:** 173–81.
5. Hommes OR, Lamers KJB, Reeks P. Effect of intensive immunosuppression on the course of chronic progressive multiple sclerosis. *J Neurol* 1980; **223:** 177–90.
6. Hauser SL, Dawson DM, Lehrich JR, et al. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. *N Engl J Med* 1983; **308:** 173–80.
7. Khatri BO, McQuillen MP, Harrington GJ, Schmoll D, Hoffmann RG. Chronic progressive multiple sclerosis: double-blind controlled study of plasmapheresis in patients taking immunosuppressive drugs. *Neurology* 1985; **35:** 312–19.
8. Goodkin DE, Plencner S, Palmer-Saxerud J, Teetzen M, Hertsgaard D. Cyclophosphamide in chronic progressive multiple sclerosis maintenance vs nonmaintenance therapy. *Arch Neurol* 1987; **44:** 823–27.
9. Carter JL, Hafler DA, Dawson DM, Orav J, Weiner HL. Immunosuppression with high-dose i.v. cyclophosphamide and ACTH in progressive multiple sclerosis: cumulative 6-year experience in 164 patients. *Neurology* 1988; **38:** 9–14.
10. Mackin GA, Weiner HL, Orav JA, et al. IV cyclophosphamide/ACTH plus maintenance cyclophosphamide boosters in progressive MS: interim report of the Northeast Cooperative MS Treatment Group. *Neurology* 1990; **40** (suppl 1): 260.
11. Cook SD, Devereux C, Troiano R, et al. Effect of total lymphoid irradiation in chronic progressive multiple sclerosis. *Lancet* 1986; i: 1405–09.
12. The Multiple Sclerosis Study Group. The efficacy and toxicity of cyclosporine A in chronic progressive multiple sclerosis: a randomized, double-blinded, placebo-controlled clinical trial. *Ann Neurol* 1990; **27:** 591–605.
13. Rudge P, Koetsier JC, Mertin J, et al. Randomized double blind controlled trial of cyclosporin in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1989; **52:** 559–65.
14. Mertin J, Rudge P, Kremer M, et al. Double-blind controlled trial of immunosuppression in the treatment of multiple sclerosis: final report. *Lancet* 1982; ii: 351–54.
15. Hughes RAC. Immunological treatment of multiple sclerosis I. *J Neurol* 1983; **230:** 73–80.
16. British and Dutch Multiple Sclerosis Azathioprine Trial Group. Double-masked trial of azathioprine in multiple sclerosis. *Lancet* 1988; ii: 179–83.
17. Ellison GW, Myers LW, Mickey MR, et al. A placebo-controlled, randomized, double-masked, variable dosage, clinical trial of azathioprine with and without methylprednisolone in multiple sclerosis. *Neurology* 1989; **39:** 1018–26.
18. Rose AS, Ellison GW, Myers LW, Tourtellotte WW. Criteria for the clinical diagnosis of multiple sclerosis. *Neurology* 1976; **26:** 20–22.
19. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; **13:** 227–31.
20. Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; **33:** 1444–52.
21. Noseworthy JH, Shumak KH, Vandervoort MK. Long-term use of antecubital veins for plasma exchange. The Canadian Cooperative Multiple Sclerosis Study Group. *Transfusion* 1989; **29:** 610–13.
22. Noseworthy JH, Vandervoort MK, Ebers GC. Acceptance of placebo-control trial design by progressive multiple sclerosis patients. The Canadian Cooperative Multiple Sclerosis Study Group. *Neurology* 1989; **39:** 606–07.
23. Breslow NE. A generalized Kruskal-Wallis test for comparing k samples subject to unequal patterns of censorship. *Biometrika* 1970; **57:** 579–94.
24. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53:** 457–81.
25. Kurtzke JF. Neuroepidemiology. Part II: assessment of therapeutic trials. *Ann Neurol* 1986; **19:** 311–19.
26. Noseworthy JH, Vandervoort MK, Hopkins B, Ebers GC. A referendum on clinical trial research in multiple sclerosis: the opinion of the participants at the Jekyll Island workshop. *Neurology* 1989; **39:** 977–81
27. Shumak KH, Rock GA. Therapeutic plasma exchange. *N Engl J Med* 1984; **310:** 762–71.
28. Ehrke MJ, Mihich E, Berd D, Mastrangelo MJ. Effects of anticancer drugs on the immune system in humans. *Semin Oncol* 1989; **16:** 230–53
29. Chabner BA, Myers CE. Clinical pharmacology of cancer chemotherapy. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer. Principles and practice of oncology. Philadelphia: JB Lippincott, 1989: 369–71.
30. Likosky WH. Experience with cyclophosphamide in multiple sclerosis: the cons. *Neurology* 1988; **38** (suppl 2): 14–18.
31. Weinshenker BG, Bass B, Rice GPA, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain* 1989; **112:** 133–46.
32. Miller A, Drexler E, Keilson M, et al. Spontaneous stabilization in patients with progressive MS. *Neurology* 1988; **38** (suppl 1): 194.
33. Coronary Drug Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project. *N Engl J Med* 1980; **303:** 1038–41.
34. Noseworthy JH, Vandervoort MK, Wong CJ, Ebers GC and the Canadian Cooperative MS Study Group. Interrater variability with the expanded disability status scale (EDSS) and functional systems (FS) in a multiple sclerosis clinical trial. *Neurology* 1990, **40:** 971–75
35. Weinschenker BG, Rice GPA, Noseworthy JH, et al. The natural history of multiple sclerosis. A geographically based study. IV. Applications to planning and interpretation of clinical therapeutic trials. *Brain* (in press).

From The Lancet

Petits pois?

A sub-committee was appointed by the Glasgow Town Council a few months since to inquire into the greening of French vegetables with sulphate of copper. The committee approved of the report which was presented to them, and recommended that intimation be made to dealers in canned vegetables that the sanitary officials would institute proceedings whenever the circumstances in connexion with their re-greening were sufficient to warrant a prosecution. The report is signed by the medical officer of health, the sanitary inspector, and the analysts of the city, who, in the evidence they furnish, quote the opinions of the French authorities upon the subject. That preserved peas are in many instances greened by means of a salt of copper seems well established. This treatment with copper salt, it may be remarked, is not at all necessary for the preservation of the vegetables. Sealing them up hermetically after exposure for a time to a temperature above boiling-point is all that is required. . . . The cultivation of vegetables such as peas in this country, it is pointed out, is considerably handicapped by the substitution of the re-greened, stale, and probably less digestible article of foreign growth, which there is good reason to suppose is not infrequently palmed off as the genuine, fresh, home-grown product. The majority of those who have any concern in the important question of food in its relation to health will share generally in the views which are expressed by the medical officer of health, sanitary inspector, and the analysts of the city of Glasgow in the concluding sentences of their report. They are of the opinion that the process of re-greening is fraudulent in its intention and injurious in its commercial results; that re-greening with sulphate of copper does not make vegetables more but probably less wholesome; that the public ought when purchasing preserved vegetables to ask for ungreened or at least vegetables free from copper; that the guardians of the public health ought to come to an understanding as to the sale of vegetables containing copper, while holding themselves free to act according to the circumstances of the case and the scientific evidence obtainable from time to time.

(Jan 31, 1891)