# Cyclosporine Versus Azathioprine in the Long-Term Treatment of Multiple Sclerosis—Results of the German Multicenter Study

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**In a double-blind controlled trial of 194 patients with clinically definite active multiple sclerosis, 98 were randomized to treatment with cyclosporine (CyA, 5 mg/kg/day), and 96 to treatment with azathioprine (Aza, 2.5 mg/kg/day). Eighty-five patients in the CyA group and 82 in the Aza group completed a treatment period of 24 to 32 months in accordance with the study protocol. No significant differences could be detected between the two treatment groups at the end of the trial. Assessment was done by serial quantitative neurological examinations and Kurtzke's Expanded Disability Status Scale. Frequency of relapse and patient self-evaluation also failed to show significant differences. Overall deterioration observed in both groups during the trial was only minor. The incidence of side effects in the CyA group was more than two times that in the Aza group. We conclude that CyA as a single agent cannot be the drug of final choice in long-term immunosuppressive treatment of relapsing-remitting and relapsing-progressive multiple sclerosis.**

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Cyclosporine (CyA), a cyclic undecapeptide with a molecular weight of 1,206 [35], is the prototype of a new generation of immunosuppressive agents [2]. It exhibits a selective and reversible effect on lymphocytes without being directly antiproliferative [45].

Although the exact mode of action is not known, experimental evidence suggests that it inhibits transcription of messenger RNA encoding for lymphokine production [9, 15, 24]. Synthesis of IL2 (T-cell growth factor), gamma interferon, and B-cell and cytolytic T-cell stimulating factors is suppressed [4]. As a result of this suppressive effect, CyA inhibits helper and cytolytic T-cell function in both primary immunization and ongoing immune reactions [9, 15]. A further advantage of CyA is our ability to monitor its blood level [7]. In clinical transplantation CyA has brought about clear-cut improvement in results [29, 39].

In animal experiments CyA has been effective in both preventing and suppressing autoimmune encephalomyelitis [3], a model for multiple sclerosis (MS) in which autoreactive T-helper cells are the pathogenic vehicle [43]. Although reports of elevated T helper/T suppressor ratios in the peripheral blood of patients with active MS are controversial [36, 37], the use of CyA, an agent that selectively acts on T-helper function, was even more attractive.

In the present study CyA is compared with azathioprine (Aza), a drug used in our centers [6, 33] as standard immunosuppressive treatment for patients with relapsing-remitting or relapsing-progressive MS. Although evidence from past therapeutic trials is contradictory concerning the efficacy of Aza [10, 19, 26, 33], we believed that CyA should show a better risk/benefit ratio than Aza if it was to be recommended for the long-term treatment of MS.

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## Methods

The trial protocol was approved by the ethics committees of the medical faculties in Hannover and Würzburg. The study was conducted in accordance with the requirements of the declaration of Helsinki.

### *Patient Population and Recruitment*

Patients with a diagnosis of clinically definite MS according to the criteria of Schumacher and co-workers [40] were included in the study if they met the following criteria: elevated autochthonous IgG production in the central nervous system and/or oligoclonal bands in the cerebrospinal fluid; active disease during the past two years (either well-documented occurrence of more than one relapse per year or deterioration of one or more grades in Kurtzke's Expanded Disability Status Scale [EDSS {27}] during the year prior to recruitment); age between 18 and 50 years; no other immunosuppressive treatment during the last two years (patients treated with Aza were admitted without washout); EDSS Grades 0 to 6.5 (ambulatory patients); an interval of at least 10 weeks between the start of the last relapse and inclusion in the study (this interval was a compromise between avoidance of the initial spontaneous improvement that usually follows a relapse and our intention not to exclude patients with frequent relapses); no medical illnesses or psychic alterations judged incompatible with safe administration of the treatment regimens; and good compliance.

Between May 1983 and March 1984, 196 patients were recruited for the trial in both centers. Two patients withdrew before the treatment had begun and will not be further mentioned. Ninety-eight patients were randomized to CyA treatment and 96 to Aza treatment according to a stratified randomization schedule. Both treatment groups were comparable in terms of age, disease duration, course, neurological deficit at entry, proportion of patients pretreated with Aza, and mean intelligence quotient; only the sex ratio was somewhat different, with relatively fewer women in the CyA group (Table 1).

Patients were divided into three categories according to the course of their disease (Table 1): The relapsing-remitting category included patients with complete remissions (EDSS score lower than 2.0) between exacerbations (n = 25; 9 CyA, 16 Aza) and those with only partial remissions and hence accumulating neurological deficit (n = 98, 54 Cya, 44 Aza). The relapsing-progressive category included patients with both progression and superimposed attacks. The chronic progressive category included patients with steady progression without exacerbations.

*Table 1. Background Data of the Patients Recruited*

| Background | Cyclosporine Group (n = 98) | Azathioprine Group (n = 96) |
|---|---|---|
| | No. (%) | No. (%) |
| Sex | | |
| Male | 39 (40) | 29 (30) |
| Female | 59 (60) | 67 (70) |
| Age, mean (SD) | 35.5 (8.4) | 34.7 (9.0) |
| Disease duration (yr), mean (SD) | 6.1 (5.1) | 7.2 (6.9) |
| Course of disease | | |
| Relapsing-remitting | 63 (64) | 60 (63) |
| Relapsing-progressive | 21 (21) | 25 (26) |
| Chronic progressive | 14 (15) | 11 (11) |
| Disease severity[a] | | |
| 0–2.5 | 45 (46) | 44 (46) |
| 3–4.5 | 36 (37) | 34 (35) |
| 5–6.5 | 17 (17) | 18 (19) |
| Pretreatment with azathioprine | 26 (27) | 27 (28) |
| Treatment center | | |
| Würzburg | 52 (53) | 54 (56) |
| Hannover | 46 (47) | 42 (44) |
| IQ, mean (SD) | 99 (13) | 98 (14) |

[a] As measured by Kurtzke's Expanded Disability Status Scale.

### *Medication and Monitoring of Compliance*

Patients and all the physicians directly involved in the care and evaluation of the patients were masked for treatment group. Only the physician responsible for the laboratory monitoring and the study nurse in each center were informed of treatment group.

One patient group received CyA drinking solution (5 mg/kg/day) and placebo capsules; the other received placebo drinking solution and Aza capsules (2.5 mg/kg/day); each program was indistinguishable from the other.

The dosage of Cya was adjusted to obtain trough whole-blood CyA levels between 200 and 1,000 ng/ml. The therapeutic range was lowered to values between 150 and 750 ng/ml after the first 9 months of the study because of further data provided by Sandoz AG from other trials [14]. In the Aza-treated group the dosage was increased stepwise if the mean corpuscular volume of the erythrocytes did not exceed the upper limit of normal after 6 months of treatment. It was reduced by 25% if the leukocyte count fell more than 500/mm$^3$ below the normal limit. Medication was also reduced when the creatinine values were greater than 130 μmoles/liter, when liver enzymes exceeded the upper limit of normal, or when other severe side effects were observed either clinically or through laboratory tests.

Physical therapy and other symptomatic treatments excluding immunosuppressants were prescribed at the discretion of the attending neurologist. Relapses were treated with corticosteroids according to a standardized schedule, starting with 100 mg of prednisone daily and tapering over 8 weeks.

### *Clinical Assessment*

Before treatment and every 3 months during the study a complete neurological evaluation was performed using well-known scales: EDSS [27], Functional Systems [27], Incapacity Scale [20], Hauser's Ambulation Index [16], and "Neurostatus," a quantitative neurological examination specially developed for this study that is similar to the scales used by Fog [12] and Patzold and Weinrich [33]. The number of relapses was also assessed. We defined relapse as the deterioration of existing status or the occurrence of new symptoms for at least 4 days after a period of remission or stabilization of at least 4 weeks. Each neurological evaluation, including the initial one, was performed by the same neurol-

ogist, who had no access to the results of previous examinations. Patients in Würzburg were evaluated by U. P. from Hannover and S. P. from Göttingen, patients in Hannover by L. K. and D. D. from Würzburg. A detailed self-evaluation questionnaire was completed quarterly by the patients [23]. They all underwent serial electrophysiological and immunological studies (data to be published separately).

*Monitoring of Adverse Events*

The monthly safety examinations included complete blood count and differential, platelet count, erythrocyte sedimentation rate, automated chemistry profiles of serum, urinalysis, and CyA trough whole blood levels (radioimmunoassay provided by Sandoz). A physical examination including pulse rate and blood pressure measurements was performed at each 3-month visit by the attending neurologist, who registered side effects and rated them on a 3-point scale (mild, moderate, severe). Adverse events were registered even if they were mild and their relationship to the treatment was considered vague. For the calculation of incidence, each side effect was counted only once per patient, regardless of how long it lasted. For the calculation of overall frequency, each different event was counted once every 3 months.

*Statistical Analysis*

The two main criteria for the statistical analysis were the total Neurostatus scores and EDSS scores. The scores of each patient were approximated by fitting third-order orthogonal polynominals. The four corresponding coefficients (constant, linear, quadratic, and cubic) were estimated using ordinary least squares regression. The constant term reflects the extent of neurological deficit, the linear coefficient is a measure of the progression of the disease (linear trend), and the quadratic and cubic coefficients describe the deviation of disease course from linearity. If the sum of the quadratic and cubic is high in comparison to the sum of the constant and linear polynominals, the course of the disease is markedly nonlinear; if the quadratic is higher than the cubic polynomial, the course of the disease has a more convex or concave shape; if the contrary is true, the course of the disease has a more oscillating shape [8, 13, 32, 33]. For each patient the four coefficients give a concise description of the course of the disease during the observation period. The intergroup comparisons of each of the four coefficients were done by applying the Wilcoxon-Mann-Whitney rank sum test, comparisons of nominal data and frequencies by the $\chi^2$ test (all tests two-tailed) [42].

*Power of the Trial*

Applying the formula of Neyman [42] and the standard deviation observed during the study and assuming as relevant a mean difference of one point in the EDSS [27] and an alpha of 5%, the calculated beta was 10%, as was foreseen in the sample size calculation for this trial.

## Results

Eighty-five CyA- and 82 Aza-treated patients completed at least 24 months of treatment according to the protocol; these will be referred to as valid patients. Twelve patients (6 CyA, 6 Aza) were considered dropouts because of noncompliance (4 CyA, 4 Aza), wish to become pregnant (1 CyA, 2 Aza), or moving away (1 CyA). Seven CyA- and 8 Aza-treated patients were withdrawn because of deterioration in neurological status (4 CyA), gastrointestinal intolerance (1 CyA, 7 Aza), bad taste of medication (1 CyA), hepatotoxicity (1 CyA), and prolonged leukopenia (1 Aza).

*Table 2. Changes in Neurological Deficit*

| | Valid Patients[a] | | Dropouts[b] | | Withdrawals[b] | |
|---|---|---|---|---|---|---|
| Condition | CyA | Aza | CyA | Aza | CyA | Aza |
| Better | 17 | 13 | 1 | 2 | 0 | 1 |
| Stable[c] | 49 | 48 | 5 | 3 | 3 | 7 |
| Worse | 19 | 21 | 0 | 1 | 4 | 0 |
| All | 85 | 82 | 6 | 6 | 7 | 8 |

[a]Baseline compared to month 24.
[b]Baseline compared to the time of discontinuation.
[c]Change of less than 1 point on Kurtzke's Expanded Disability Status Scale.

CyA = cyclosporine; Aza = azathioprine.

The mean of all individual mean CyA blood levels of valid CyA-treated patients during the 24 months of treatment was 269 ng/ml (range, 69 to 483 ng/ml, SD 77). Seven patients in the first year and 12 in the second year had mean CyA blood levels below 150 ng/ml. Only two patients in the Aza group had normal mean corpuscular volume of the erythrocytes and leukocyte counts throughout the treatment period. The clinical response to treatment in terms of neurostatus, EDSS, Incapacity Scale, and Ambulation Index is summarized in Tables 2 and 3 and the Figure. No significant difference could be found between the two treatment groups, either by applying a $\chi^2$ test on categorized changes from baseline or by subjecting the estimated regression coefficients, separately for each of the four terms, to a Wilcoxon-Mann-Whitney test. Neither the constant nor the linear term (Table 4) showed any significant difference between the two treatment groups, nor did the quadratic and cubic terms (data not shown). The same was true for different groups of patients divided according to course and duration of disease. There was no significant correlation between the mean CyA whole blood level and disease progression as determined by linear regression. Even if patients with no more than one CyA blood level per year below 150 ng/ml were evaluated separately ("good compliers"), the results did not differ.

The number of relapses in each group was not significantly different. In the first year of treatment the mean annual relapse rate was 0.36 (SE, 0.07) in CyA- and 0.32 (SE, 0.06) in Aza-treated patients; in the second year rates were 0.32 (SE, 0.07) and 0.50 (SE, 0.08), respectively. Thirty-four percent of CyA- and

*Table 3. Clinical Scores at Entry and After 24 Months*[a]

| Measure | Month 0 | | Month 24 | |
|---|---|---|---|---|
| | CyA (n = 85) | Aza (n = 82) | CyA (n = 85) | Aza (n = 82) |
| Neurostatus | 44.8 (3.6) | 44.2 (3.6) | 45.0 (4.0) | 50.2 (4.9) |
| EDSS | 3.0 (0.2) | 3.2 (0.2) | 3.1 (0.2) | 3.5 (0.2) |
| Ambulation index | 1.6 (0.1) | 1.7 (0.2) | 1.8 (0.2) | 2.0 (0.2) |
| Incapacity scale | 2.9 (0.4) | 2.7 (0.4) | 2.9 (0.4) | 3.6 (0.5) |

[a]Numbers are mean values (SEM) in valid patients; intergroup differences nonsignificant (Mann-Whitney U-test).

CyA = cyclosporine; Aza = azathioprine; EDSS = Kurtzke's Expanded Disability Status Scale.

33% of Aza-treated patients had been treated with corticosteroids. The number of corticosteroid courses prescribed was 45 in both groups. There was no apparent difference in the dosage or in the number of patients receiving symptomatic treatment. The overall estimation of treatment efficacy at the end of the study, by both investigators and patients, was nearly identical for the two drugs (Table 5).

*Efficiency of Blinding*

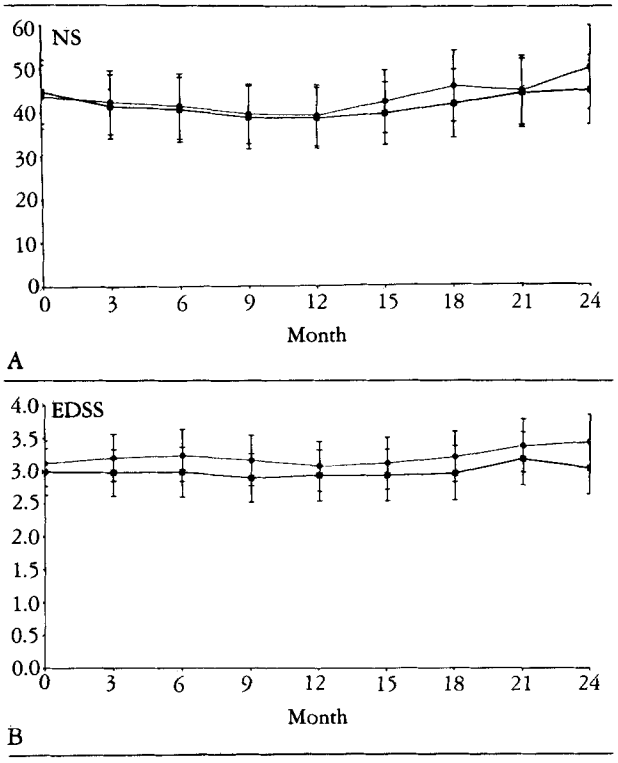
We assessed the efficiency of blinding by asking patients, examination neurologists, and treatment neurologists at the last regular visit for their opinion on what treatment had been given. The percentage of correct answers was 45, 61, and 72, respectively.

*Side Effects*

The incidences of the main side effects are shown in Tables 6 and 7. Gastrointestinal symptoms were the most frequent side effects in both treatment groups. Although their absolute number was equal in the two groups, Aza-treated patients had significantly more gastrointestinal symptoms of moderate and severe intensity, mainly epigastric pain, nausea, and vomiting. Infections occurred in both treatment groups at the same frequency and severity. In the CyA-treated group hypertrichosis, paresthesias, and gingival hyperplasia were in most cases mild and required dosage reduction in only a few. A significant increase in mean serum creatinine level was observed after 2 weeks of CyA treatment. This increase and the occurrence of hypertension were the most frequent causes of dosage reduction. Elevated blood pressure was treated by beta-blocking agents, saluretics, and dosage reduction. After the discontinuation of treatment at the end of the trial creatinine levels and blood pressure returned to normal with only a few exceptions.

During a treatment period of up to 32 months, 985 adverse events were registered in the 98 CyA-treated patients at their regular 3-month evaluations (abnormal laboratory values and blood pressure were not counted). Sixty percent of these adverse events were mild, 35% moderate, and only 5% severe. In the 96 Aza-treated patients, 485 adverse events were recorded (60% mild, 34% moderate, and 6% severe).

Life-threatening or disabling adverse events did not occur, with one exception. A 43-year-old woman with a history of epileptic seizures had a series of convulsions after 3 months of treatment and developed aspiration pneumonia and severe hypoxic brain damage. At that time she had CyA blood levels below the range thought to be therapeutic.




*Neurological deficit versus length of treatment. Mean scores with 95% confidence intervals in valid patients (n = 167). Solid line with squares = cyclosporine (n = 85); dotted line with circles = azathioprine (n = 82). (A) Quantified neurological examination (Neurostatus, NS). (B) Expanded Disability Status Scale (EDSS).*

*Table 4. Disease Progression During the 24-Month Treatment as Determined by Polynomial Approximation*[a]

| Disease Category | Cyclosporine n | Cyclosporine Neurostatus | Cyclosporine EDSS | Azathioprine n | Azathioprine Neurostatus | Azathioprine EDSS |
|---|---|---|---|---|---|---|
| All valid patients | 85 | | | 82 | | |
| Constant term[b] | | 41.9 (3.6) | 3.0 (0.2) | | 43.5 (3.7) | 3.2 (0.2) |
| Linear term[c] | | 0.6 (0.8) | 0.1(0.05) | | 2.9 (1.2) | 0.1 (0.05) |
| Relapsing-remitting | 52 | | | 51 | | |
| Constant term | | 30.4 (4.3) | 2.4 (0.2) | | 30.9 (3.7) | 2.7 (0.2) |
| Linear term | | 0.2 (1.0) | 0.1 (0.07) | | 2.3 (1.7) | 0.1 (0.07) |
| Relapsing-progressive | 20 | | | 22 | | |
| Constant term | | 54.6 (5.9) | 3.7 (0.3) | | 68.3 (7.3) | 4.2 (0.3) |
| Linear term | | −1.0 (1.8) | 0.1 (0.1) | | 3.6 (2.0) | 0.2 (0.1) |
| Chronic progressive | 13 | | | 9 | | |
| Constant term | | 68.0 (8.7) | 4.3 (0.4) | | 54.7 (10.7) | 4.0 (4.7) |
| Linear term | | 4.7 (2.4) | 0.2 (0.08) | | 4.2 (2.3) | 0.3 (0.1) |

[a]Values are mean (SEM).
[b]The constant part of the polynomial reflects disease severity at onset.
[c]The linear term of the polynomial reflects disease progression during the treatment period.

EDSS = Kurtzke's Expanded Disability Status Scale.

*Table 5. Overall Treatment Efficacy as Assessed by Patients and Investigators at the End of the Trial*

| Assessor | Drug | Overall Efficacy None | Slight | Moderate | Good | Very Good |
|---|---|---|---|---|---|---|
| Patient | CyA | 28 | 11 | 11 | 26 | 6 |
| | Aza | 24 | 14 | 7 | 31 | 6 |
| Investigator | CyA | 18 | 16 | 22 | 23 | 6 |
| | Aza | 18 | 13 | 21 | 26 | 4 |

CyA = cyclosporine; Aza = azathioprine.

*Table 6. Incidence of Clinical Side Effects*[a]

| Side Effect | Cyclosporine (n = 98) | Azathioprine (n = 96) |
|---|---|---|
| | No. (%) | No. (%) |
| Gastrointestinal (gastric pain, nausea, vomiting, loss of appetite, weight decrease) | 54 (55) | 53 (55) |
| Infections (viral, bacterial, fungal) | 53 (54) | 48 (50) |
| Hypertrichosis | 49 (50) | 14 (15) |
| Gingival hyperplasia/gingivitis | 33 (34) | 11 (11) |
| Paresthesias | 32 (33) | 7 (7) |
| Hair loss | 13 (13) | 15 (16) |
| Headache | 18 (18) | 5 (5) |
| Skin eruptions | 11 (11) | 9 (9) |
| Tremor | 6 (6) | 0 |
| Seizures | 3 (3) | 0 |
| Weight/appetite increase | 5 (5) | 8 (8) |
| Joint/limb/skeletal pain | 7 (7) | 1 (1) |

[a]Number (%) of patients affected during a treatment period of up to 32 months.

*Table 7. Incidence of Abnormal Laboratory Values and Hypertension*[a]

| Value | Cyclosporine (n = 98) | Azathioprine (n = 96) |
|---|---|---|
| | No. (%) | No. (%) |
| Serum creatinine (increased) | 35 (36) | 3 (3) |
| Gamma glutamyltransferase | 19 (19) | 23 (24) |
| Transaminase (GPT) | 24 (24) | 33 (34) |
| Raised erythrocyte MCV | 58 (59) | 81 (84) |
| Leukopenia | 8 (8) | 51 (53) |
| Anemia (low hemoglobin) | 75 (76) | 63 (66) |
| Elevated blood pressure (diastolic) | 38 (39) | 11 (11) |
| Elevated blood pressure (systolic) | 13 (13) | 5 (5) |

[a]Number (%) of patients with two or more abnormal laboratory values at different monthly examinations; two or more blood pressure values exceeding 90 mm Hg (diastolic) or 150 mm Hg (systolic) at separate 3-month safety examinations; first 24 months of the treatment.

MCV = mean corpuscular volume.

## Discussion

To our knowledge, this is the first completed large-scale, controlled trial of CyA treatment for MS. No perceivable difference in clinical neurological outcome could be found between the two treatment groups. In this study CyA did not exhibit the same advantages as it had in transplantation [29, 39].

The patients we studied had mainly relapsing-remitting and relapsing-progressive MS (see definitions in the Methods section). Although we studied only patients with active disease in the two years preceding recruitment, the disease course of these two groups of patients is by definition less predictable than that of patients with a chronic progressive course. The number of patients with chronic progressive disease included in the study does not allow a valid answer concerning this subgroup of patients. We thought that the sample size and the length of the treatment period would compensate for this inherent unpredictability and would allow us to recognize an existing difference in neurological outcome. The a posteriori statistical power estimation seems to support this view, but it may be argued that even longer observation periods and even larger samples are required for patients with a relapsing-remitting or relapsing-progressive course.

Were the patients not sufficiently treated? Compliance was monitored thoroughly by CyA blood level determinations and mean corpuscular volume changes (Aza) and was very good in the great majority of the patients. Was the CyA concentration too low? Although we used a lower dosage than formerly administered to patients undergoing transplantation, it was in the range recently proposed for the treatment of autoimmune disease [14] and for long-term treatment after transplantation [1, 22]. Patients with higher mean CyA levels did not differ in outcome from patients with lower levels. Even with this relatively low dosage of CyA, we observed a considerable number of side effects. Was CyA not reaching the demyelinating lesions in the central nervous system in sufficient amounts? In spite of its lipophilic structure CyA seems to penetrate the blood-brain barrier poorly, probably because of its high molecular weight. Postmortem CyA concentrations in the brains of patients who had undergone transplantation and had been treated with CyA have been consistently low [38]. In the cerebrospinal fluid CyA was either undetectable [31] or in a concentration 100 times less than in whole blood (unpublished observations). It is not clear if the therapeutic effect of immunomodulating or immunosuppressive agents is primarily the result of their systemic action or their local action in the central nervous system. Experimental evidence on lymphocyte migration and antigen recognition within the central nervous system [44] as well as a report on the efficacy of total lymphoid irradiation (excluding the neuraxis) [5] seem to support the former. Alternatively, are those steps of the immune response that are influenced by CyA of only minor or no importance in the pathogenesis of MS? As long as the presumed autoimmune pathogenesis of MS is incompletely understood [28], this question must also remain unanswered.

This study is the first, to our knowledge, that describes the long-term side effects of CyA in a double-blind setting in a large, homogeneous group of patients without major vascular or renal risk factors. The occurrence of hypertrichosis, paresthesias, and gingivitis in Aza-treated patients as well as hair loss in the CyA-treated group can be interpreted as an indicator of efficient blinding of both investigators and subjects. Hypertrichosis could have been partly attributed to the additional corticosteroid medication some of the patients received for exacerbations. Qualitatively the observed side effects were similar to those reported during the treatment of patients undergoing transplantation [25], but the overall incidence seems to be higher in our study, perhaps because the treatment period was long (24 to 32 months) and we tended to record even mild complaints and symptoms. The similar frequency and severity of infections in both treatment groups contrasted with some previous reports describing a reduced rate of infection in CyA-treated patients [17, 18]. Perhaps this discrepancy results because in most studies CyA has been compared to combinations of Aza and corticosteroids or other immunosuppressive agents. Elevated blood pressure and creatinine levels (not always related to each other) were the most serious complications seen in the CyA-treated group. Both side effects tended to normalize after discontinuation of CyA. The meticulous monitoring of blood levels and side effects in this study seems to have detected patients in whom serious complications might have occurred if a higher CyA dosage had been maintained. Higher blood levels probably would have resulted in more severe and perhaps permanent nephrotoxicity or hypertension [14]. In view of these side effects, only a clear-cut advantage in favor of CyA would allow its use as the first choice in the treatment of MS.

Although the overall deterioration observed during the trial was negligible in both treatment groups, considering the lack of a placebo group, this study cannot state definitely whether either of the two drugs is effective in the treatment of MS. A recently completed double-blind trial comparing Aza with placebo and a combination of Aza and methylprednisolone showed only a tendency in favor of Aza as a single therapy; only Aza plus methylprednisolone resulted in a significant reduction of disease progression [11]. Another multicenter trial comparing Aza with placebo for individual treatment periods of 3 years is under way in Great Britain [19] and will be completed during 1987.

The not yet completed large cooperative study in the United States comparing CyA with placebo is focused on patients with more severe chronic progressive disease. It and the smaller English-Dutch trial that also compares CyA with placebo [40] should provide valuable complementary information on the usefulness of CyA in MS [21].

In our opinion, if CyA is to play a role in future treatment for MS, a more reasonable risk/benefit ratio should be established; either by the development of less nephrotoxic compounds or by the combination of low-dose CyA with other agents having an additive or complementary action on the immune system.

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