Cladribine and progressive MS

Clinical and MRI outcomes of a multicenter controlled trial

George P.A. Rice, MD, for the Cladribine Clinical Study Group*; and Massimo Filippi, MD, and Giancarlo Comi, MD, for the Cladribine MRI Study Group*

Article abstract—*Objective:* To evaluate the safety and efficacy of two doses of cladribine in patients with progressive MS. *Background:* Treatment of progressive MS patients with cladribine in a previous single-center, placebo-controlled clinical trial was associated with disease stabilization. *Methods:* In the current study, 159 patients with a median baseline Kurtzke's Expanded Disability Status Scale (EDSS) score of 6.0 were randomly assigned to receive placebo or cladribine 0.07 mg/kg/day for 5 consecutive days every 4 weeks for either two or six cycles (total dose, 0.7 mg/kg or 2.1 mg/kg, respectively), followed by placebo, for a total of eight cycles. Thirty percent had primary progressive MS (PPMS) and 70% had secondary progressive MS (SPMS). EDSS and Scripps Neurologic Rating Scale (SNRS) scores were assessed bimonthly and MRI was performed every 6 months. The primary outcome measure was disability (mean change in EDSS). *Results:* Mean changes in disability did not differ among the groups at the end of the 12-month double-blind phase. Both cladribine treatments were superior to placebo for the proportion of patients having gadolinium-enhanced T1 lesions and for the mean volume and number of such lesions ($p \leq 0.003$). Differences were statistically significant at the 6-month evaluation time, with ≥90% reduction in volume and number of enhanced T1 lesions, which was maintained through final evaluation. This effect segregated largely with the SPMS group. The T2 burden of disease showed a modest improvement in cladribine-treated patients and worsened in placebo-treated patients. Most adverse events were mild or moderate in severity and not treatment limiting. *Conclusion:* No significant treatment effects were found for cladribine in terms of changes in EDSS or SNRS scores. Both doses of cladribine produced and sustained significant reductions in the presence, number, and volume of gadolinium-enhanced T1 brain lesions on MRI, and cladribine 2.1 mg/kg reduced the accumulation of T2 lesion load. Cladribine at doses up to 2.1 mg/kg was generally safe and well tolerated. **Key words:** Cladribine—MRI—Progressive MS—Suppression of disease activity.

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With the exception of trauma, MS—a demyelinating disease of the CNS with an estimated prevalence of 250,000 to 350,000 in the United States and 1.1 million worldwide—is the most common cause of neurologic disability in young adults.[1] About two thirds of patients develop a relapsing-remitting pattern (RRMS), and the majority of these will experience a progressive deterioration, or secondary progressive MS (SPMS); about 15% of patients appear to have a progressive course from onset, or primary progressive MS (PPMS).[2] The mandate for prevention of disease progression is compelling. The natural history of progressive MS has been little altered, at least in the short term, by currently available agents. β-Interferons have been reported to be effective in the treatment of RRMS,[3-13] and recently, interferon β-1b has been reported to delay the time to confirmed progression in patients with SPMS by 9 to 12 months.[14]

MRI has allowed direct visualization of the number, location, and volume of acute and chronic lesions associated with underlying disease pathology, and some correlations between MRI and clinical parameters have been demonstrated.[15] In patients with RRMS and SPMS, there is a correlation between the frequency and extent of lesion enhancement and short-term disease activity.[16-19] In clinical trials, the presence of contrast-enhanced T1 lesions at baseline has been shown to predict both clinical and MRI activity in the following 6 months,[19] and, in patients with clinically isolated syndromes suggestive of MS, T2 lesion load at presentation is strongly correlated with disability after 5 years.[20,21] A recent meta-analysis of data from nine studies in 307 patients with RRMS and SPMS, however, found that although enhancement predicts the occurrence of relapses it is not a strong predictor of subsequent accumulation of disability over a 2-year period of observation.[22] Phase III clinical trials evaluating new therapies for MS now almost always include MRI evaluations along with traditional clinical assessments.[15,23]

Cladribine (2-chlorodeoxyadenosine; 2-CdA) is a purine nucleoside analogue resistant to the action of

*See Appendix 1 on page 1154 for a listing of members of the Cladribine Study Group and the Cladribine MRI Study Group.

From the University Hospital (Dr. Rice), University of Western Ontario, London, Canada; and the Neuroimaging Research Unit (Dr. Filippi) and Clinical Trials Unit (Dr. Comi), Department of Neuroscience, Scientific Institute Ospedale San Raffaele, University of Milan, Italy.

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Address correspondence and reprint requests to Dr. Rice, LHSC-UC, 339 Windermere Road, London, Ontario N6A 5A5, Canada; e-mail: grice@julian.uwo.ca

adenosine deaminase, which results in preferential lymphocytotoxicity. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase (e.g., lymphocytes and monocytes), cladribine is phosphorylated into the active triphosphate deoxynucleotide, 2-CdATP, which accumulates, causing a disruption of cellular metabolism, DNA damage, and subsequent cell death.[24] Its long-lasting lymphocytotoxic activity suggests that cladribine could be useful in modulating autoimmune processes involving lymphocyte abnormalities such as MS. Sipe and colleagues have reported the outcome of a placebo-controlled clinical trial of cladribine in patients with progressive MS.[25,26] Treatment with a total dose of 2.8 mg/kg cladribine was associated with significant stabilization of the disease in patients with SPMS. Compared with a progression rate of 50% of the patients treated with placebo, 95% of cladribine-treated patients were stable at 1 year. These clinical observations were supported by favorable effects in the MRI brain scans, i.e., nearly complete elimination of enhanced T1 lesions and stabilization of T2 lesion volume at final evaluation. Encouraged by this single-center study, a multicenter, double-blind, placebo-controlled trial was conducted to evaluate the safety and efficacy of two doses of cladribine in patients with progressive MS.

Methods. *Study population.* A total of 159 patients with progressive MS were enrolled at six clinical centers in the United States and Canada. Inclusion criteria for entry into the trial were clinically definite or laboratory-supported MS according to the Schumacher criteria[27] or Poser criteria[28] and defined as chronic progressive by the slow progression of signs and symptoms over the preceding 12 months; a baseline Expanded Disability Status Scale (EDSS)[29] score between 3.0 and 6.5; age 21 to 60 years; serum creatinine levels <1.5 mg/dL and creatinine clearance $\geq$ 80% of age-adjusted normal value; aspartate and alanine transaminase (AST and ALT) and alkaline phosphatase levels less than twice the normal upper limit; neutrophil count $>1600/\mu L$ and platelet count $>130{,}000/\mu L$; and clinically normal ECG and chest x-ray. Patients were excluded from the trial if there was significant history of medical disease within the preceding 2 years that would impair participation in the trial; use of corticosteroids or other immunosuppressants such as cyclophosphamide, azathioprine, cyclosporine, or β-interferon within the preceding 3 months; total lymphoid irradiation; persistent leukopenia or thrombocytopenia after treatment with immunosuppressive agents; history of alcohol or drug abuse within the preceding year or of attempted suicide; malignancy or history of malignancy within the preceding 5 years; pregnancy or nursing; positive test result for HIV; use of an experimental drug or device within the preceding 60 days; or prior participation in a trial with cladribine. The protocol was approved by the respective institutional review boards, and patients signed informed consent forms.

Study design. This multicenter trial was a randomized, double-blind, parallel-group, placebo-controlled study designed to compare the safety and efficacy of two doses of cladribine and placebo administered by subcutaneous (SC) injection in patients with progressive MS, to evaluate the dose-response relationship, and to obtain information concerning the duration of any effects. The study included a 4-week screening phase, a 1-year double-blind phase, and a 6-year long-term extension. Patients were assigned to one of three parallel treatment groups (cladribine, 2.1 mg/kg; cladribine, 0.7 mg/kg; or placebo) according to a computer-generated randomization schedule stratified by baseline disease severity and site. Sample size computation was based on an assumed SD of 1.7 for change from the baseline EDSS score. The planned sample size of 50 patients per treatment group would have a statistical power of 80% based on a two-sided alpha of 0.05 to detect a difference of 1.0 in change from the baseline EDSS score between the cladribine, 2.1 mg/kg, and placebo groups.

The trial was initiated in December 1994. During the 1-year double-blind phase, patients were evaluated monthly for vital signs, adverse events, and a complete blood count (CBC) that was obtained just before the monthly visit. Neurologic status was evaluated bimonthly by assessment of EDSS and Scripps Neurologic Rating Scale (SNRS) scores by the blinded clinical investigators, who underwent standardized training. Brain MRI scans were obtained at baseline and months 6 and 12, as were total lymphocyte count and lymphocyte subset counts ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+$ plus $CD56^+$, and $CD4^+/CD8^+$ ratio). Physical examinations were performed at baseline and months 4, 8, and 12; a chemistry panel and urinalysis were performed periodically, and an ECG was obtained at the end of the treatment phase. During the first year of the post-double-blind follow-up phase, EDSS scores, CBC, and lymphocyte counts were assessed quarterly; MRI scans were obtained at months 18 and 24.

In addition to the treating physician, an examining physician was designated at each site to assess the patient's neurologic function using EDSS and SNRS scoring. All study investigators and patients were blinded to treatment assignment; adverse events and unblinded hematology results were routinely reviewed by an independent safety monitoring board. After all patients at a study site completed the 12-month double-blind phase, the blind was broken, and patients who fulfilled the hematologic dosing criteria were permitted to receive open-label cladribine treatment during the long-term extension phase of the study, provided at least 12 months had elapsed since the last dose of cladribine and there was evidence of disease progression. Patients treated with open-label cladribine were evaluated monthly for 12 months following initiation of the drug, and then quarterly.

Study medications and dosage. Patients who met the protocol-specified entry criteria were randomized in approximately equal numbers to receive eight monthly courses of therapy. Patients received six courses of cladribine 0.07 mg/kg/day SC for 5 consecutive days (total dose, 2.1 mg/kg), followed by two courses of placebo or two courses of cladribine 0.07 mg/kg/day SC for 5 consecutive days (total dose, 0.7 mg/kg), followed by six courses of placebo or eight courses of placebo SC for 5 consecutive days. To receive a subsequent course of blinded study drug, patients were required to meet the hematologic criteria, which were based on the results of a CBC obtained 2 to 4 days before each dosing period and are listed in Appen-

dix 2. For a patient who did not meet these criteria, placebo was substituted for the active drug for that dosing period. If the hematologic criteria for dosing were met at the next evaluation, the patient received active drug the following month, up to the eighth month. All CBC data were reviewed by an independent third party. The treating physician remained blinded but was provided with any abnormal CBC results required for proper medical management.

Concomitant therapy. Methylprednisolone, 1 g/day for up to 5 days, was allowed only for treatment of severe exacerbations. In addition, patients were allowed to continue receiving symptomatic therapies to treat troublesome symptoms of MS (e.g., baclofen for spasticity or oxybutynin chloride for bladder dysfunction).

MRI evaluation. Dual-echo conventional spin-echo images were obtained using repetition times of 2500 msec and echo times of 30 (proton-density weighting) and 90 (T2 weighting) msec. T1-weighted images were obtained using repetition times of 600 msec and echo times of 20 msec. For both sequences, slices were axial with a matrix size of 256 × 256 mm and a field of view of 200 × 200 mm. Sections were 4 mm thick with a 1-mm interslice gap for the dual-echo scans and 3 mm thick and contiguous for the T1-weighted scans. The total imaging time was approximately 20 to 25 minutes. Special attention was given to careful repositioning of the patient, using laser guidance and external landmarks to help achieve reproducible slice positions. All scan data were blinded to treatment, date, and sequence of scan.

Lesion identification. *Postcontrast T1-weighted images.* A single experienced observer identified enhanced lesions following rules and criteria established in recently published guidelines.[30] Areas of enhancement were marked on transparent sheets superimposed over the scan hard copies, and then the total number of enhanced lesions per scan was counted. Corresponding dual-echo images were used to increase the confidence in lesion detection.

T2-weighted images. A single experienced observer identified hyperintense MS lesions and marked the corresponding areas on transparent sheets superimposed over the proton-density scan hard copies. Corresponding T2-weighted images were used to increase the confidence in lesion detection.

Lesion segmentation and measurement of lesion volume. Trained technicians measured the lesion volumes for the scans belonging to the same patient to avoid variabilities of interobserver measurement. A local thresholding technique was used for lesion segmentation on computer-displayed images, with the marked hard copies kept as a reference. This local thresholding technique for segmentation was provided by the Dispunc display software for MR images, developed by David Plummer (University College, London, UK). The observer first chooses a point on the lesion using a mouse-controlled cursor, and the algorithm starts contouring, following from the strongest edge point in the neighborhood of the user-selected point. This strongest edge point (i.e., the starting point) is found by searching over a 5 × 5 pixel square area with the manually selected point in its center. Once the algorithm has found the starting point, the program, searching in all directions and choosing the strongest one, finds the next contour point, which must have at least as strong a gradient as the starting point. The program then traces a contour from the most recent point, following the same principle described above; the contour is complete when it traces back to the starting point. The MS lesions detected are recorded in a file as regions of interest (ROIs) and superimposed on each image slice. The program automatically calculates the single ROI area. Manual outlining is required to modify part of the boundary of poorly defined lesions or (more rarely) to fully outline lesions not definable by contouring. The total lesion volume is then calculated, multiplying the total ROI area by the slice thickness. For the whole measurement process, the technicians followed recently published guidelines.[31]

Statistical analyses. Efficacy and safety analyses were based on the population of patients who received at least one dose of study medication and had available data. For efficacy variables, all hypothesis tests were carried out two-sided, with a significance level of <0.05 considered to be statistically significant.

The designated primary efficacy parameter was mean change in EDSS score from baseline to the final evaluation. Secondary clinical outcome measures were mean change from baseline in SNRS score and time to progression of MS. Disease progression was defined as an increase in EDSS score of ≥ 1.0 for patients with a baseline disability of 3.0 to 5.0 and an increase in EDSS score of ≥ 0.5 for patients with a baseline disability of 5.5 to 6.5, which was confirmed at the next scheduled visit. EDSS and SNRS examinations were performed by the blinded examining physician every second month during the double-blind phase. Treatment differences for the change from baseline to the final evaluation for these variables were assessed using a Wilcoxon's rank sum test. Comparisons were made between the placebo and cladribine 2.1 mg/kg groups and the placebo and cladribine 0.7 mg/kg groups, respectively. Time to progression of MS was analyzed using survival analysis methods. Kaplan-Meier estimates for the probabilities of failure were computed for each group. Log-rank tests were used to compare the distributions between the placebo and cladribine 2.1 mg/kg groups and between the placebo and cladribine 0.7 mg/kg groups.

The evaluation of MRI efficacy is based on the proportion of patients with contrast-enhanced T1-weighted brain lesions at the final evaluation. Additional MRI efficacy assessments are based on the number and volume of enhanced T1-weighted lesions and volume of T2-weighted lesions. Comparisons between treatment groups (placebo versus cladribine 2.1 mg/kg, placebo versus cladribine 0.7 mg/kg) of the proportion of patients with enhanced T1 lesions at months 6 and 12 and the final evaluation were made using Fisher's exact test. Treatment differences in enhanced T1 lesion volume and number, T2 lesion volume, and change and percent change in T2 lesion volume from baseline to final evaluation were assessed using Wilcoxon's rank sum test.

Safety analyses included summaries of adverse events. For laboratory analytes, vital signs, and body weights, means and mean changes from baseline were computed at each monthly visit.

Results. *Demographic and baseline characteristics.* The 159 eligible patients were randomly assigned to receive placebo (n = 54), cladribine 0.7 mg/kg (n = 53), or cladribine 2.1 mg/kg (n = 52). The three treatment groups

Table 1 *Demographic and baseline characteristics*

Characteristic	Placebo (n = 54)	Cladribine 0.7 mg/kg (n = 53)	Cladribine 2.1 mg/kg (n = 52)
Age, mean (y)	44.2	44.6	43.8
% Male/female	37/63	42/58	50/50
Pattern of disease			
% PPMS	26	36	29
% SPMS	74	64	71
Duration of disease (y)			
Mean	12.3	10.9	10.6
Median	11.7	10.0	8.8
EDSS score at entry			
Mean	5.6	5.6	5.6
Median	6.0	6.0	6.0
Category, % 3.0–5.0/5.5–6.5	31/69	30/70	25/75
SNRS score at entry			
Mean	60.9	60.7	62.3
Median	62.0	62.0	62.0

PPMS = primary progressive MS; SPMS = secondary progressive MS; EDSS = Expanded Disability Status Scale; SNRS = Scripps Neurological Rating Scale.

were similar with respect to age, gender, duration and pattern of disease, and baseline disability as defined by EDSS or SNRS scores (table 1). Overall, the median age was 44 years; 43% of patients were men and 57% were women. At baseline, 111 (70%) patients had SPMS and 48 (30%) patients had PPMS; 71% of patients had a baseline EDSS score of ≥5.5, indicating a population with substantial disability. Consistent with a population of more advanced disease and 30% of patients with PPMS, 63% had no enhanced lesions at baseline. Mean enhanced T1 lesion count was 1.3, and mean enhanced T1 lesion volume was 216.4 μL at baseline. Mean T2 lesion volume at baseline was 12.0 mL. Patients in the placebo group had a somewhat smaller mean enhanced T1 lesion volume than patients in the two cladribine groups (p = NS), and T1 lesion volumes at baseline had higher standard deviations among the cladribine patients than among the placebo patients.

Compliance. All 159 patients randomized to receive double-blind therapy received at least one dose of the study drug, and all are included in the efficacy analysis; 155 (97%) patients completed the double-blind phase. There were no withdrawals due to adverse events; 4 (3%) patients withdrew voluntarily from the study (subject choice) before completion of the double-blind phase (three from the low-dose cladribine group and one from the higher-dose group). The majority of patients received all eight scheduled courses of therapy (7/54 placebo-treated patients, 11/53 cladribine 0.7 mg/kg-treated patients, and 16/52 of 2.1 mg/kg-treated patients received a placebo substitution). The most common reasons for failure of the dosing criteria were fluctuations in hemoglobin levels and platelet counts, which occurred at a similar frequency in all groups.

Post-double-blind follow-up data are available for 148 of the 159 patients enrolled in the double-blind phase of this

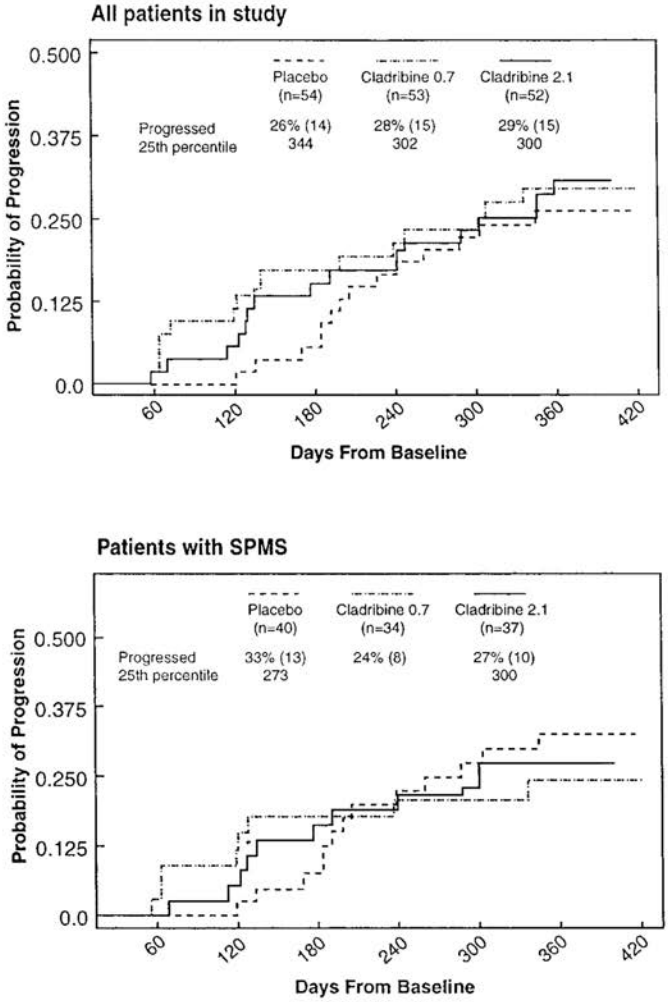

Figure 1. Probability of disease progression over time. SP = secondary progressive.

ongoing study. For the outcomes presented here, the mean duration of follow-up from the first dose was 29 months.

Clinical outcomes. During the 12-month double-blind phase, the mean changes in EDSS and SNRS scores from baseline to final evaluation were small in all three treatment arms (placebo, 0.7 mg/kg, and 2.1 mg/kg cladribine), and no differences among treatment groups were observed for placebo and cladribine. Examination of changes in EDSS scores according to pattern of disease showed that for patients with SPMS, EDSS scores increased modestly (0.3) over time in the placebo group but less in the active treatment groups (±0.0, p = NS); by comparison, very little change in EDSS score was experienced in any treatment arm by patients with PPMS. Similarly, although no significant differences among treatment groups were found in time to progression assessed by Kaplan-Meier estimate for all patients, there was a trend toward a more favorable clinical response to cladribine than to placebo in the SPMS subgroup (figure 1); 33% of patients in the placebo group met the criteria for disease progression by the end of the double-blind phase, compared with 24% to 27% of cladribine-treated patients with SPMS.

Exacerbations, steroid utilization, and hospitalizations did not differ among the three groups.

Follow-up EDSS scores obtained after the 12-month double-blind phase, but before retreatment, are available

Table 2 *Summary of MRI outcomes during double-blind phase of study: all patients*

	Placebo	Cladribine 0.7 mg/kg		Cladribine 2.1 mg/kg	
MRI parameter	n (%) or mean (SD)	n (%) or mean (SD)	*p* Value	n (%) or mean (SD)	*p* Value
Enhanced T1 lesions					
Proportion of patients with lesions (%)[a,b,d]					
Baseline	53 (38%)	52 (33%)		50 (36%)	
Month 6	51 (33%)	49 (12%)	0.0169	52 (2%)	0.001
Month 12	50 (32%)	48 (10%)	0.0131	48 (6%)	0.0017
Final evaluation	54 (31%)	51 (10%)	0.0080	52 (6%)	0.0009
Mean number of lesions (SD)[a,c,d]					
Baseline	1.17 (2.23)	1.64 (4.43)		1.10 (2.07)	
Month 6	0.78 (1.49)	0.17 (0.52)	0.008	0.12 (0.85)	<0.001
Month 12	0.57 (1.10)	0.13 (0.40)	0.007	0.09 (0.35)	0.001
Final evaluation	0.58 (1.12)	0.12 (0.39)	0.005	0.08 (0.34)	0.001
Mean volume of lesions in μL (SD)[a,c,d]					
Baseline	142.66 (302.15)	283.82 (803.10)		235.24 (777.94)	
Month 6	78.67 (168.07)	12.44 (44.35)	0.008	19.40 (137.18)	<0.001
Month 12	67.76 (119.65)	10.94 (39.99)	0.005	6.36 (26.63)	0.001
Final evaluation	78.11 (155.74)	10.28 (38.83)	0.003	5.98 (25.85)	0.001
T2 lesions					
Mean lesion volume (mL) (SD)[a,c,d]					
Baseline	12.90 (12.35)	13.03 (12.37)		9.91 (8.50)	
Month 6	13.45 (12.77)	13.15 (12.09)	0.872	9.78 (8.60)	0.155
Month 12	13.13 (13.11)	12.62 (11.52)	0.944	9.79 (8.80)	0.231
Final evaluation	13.31 (13.00)	12.65 (11.96)	0.868	9.71 (8.56)	0.180
Change from baseline to final evaluation[c,d,e]					
Mean (SD)	0.41 (1.72)	−0.39 (1.70)		−0.20 (1.13)	
Median	0.10	−0.01	0.055	−0.13	0.040
Percent change from baseline to final evaluation[c,d,e]					
Mean (SD)	1.81 (11.38)	−1.67 (14.98)		−3.93 (14.80)	
Median	1.53	0.03	0.144	−2.51	0.029

[a] Includes patients with both baseline and final evaluations.
[b] Fisher's exact test (two-sided significance).
[c] Based on Wilcoxon's (Mann-Whitney) rank sum test.
[d] The final evaluation is the last evaluation for each patient up to month 12 during year 1.
[e] Positive change indicates disease progression.

through month 24 for a sizable cohort of patients, although cohort sizes became smaller as some patients entered retreatment during the follow-up phase. Although mean EDSS scores increased over time in all treatment groups, scores for the follow-up period were also analyzed by pattern of disease. For patients with SPMS, mean changes in EDSS scores were somewhat more favorable with cladribine (0.2 and 0.3, respectively, for the 0.7-mg/kg and 2.1-mg/kg doses) compared with placebo (0.6) by 24 months. No difference was observed for patients with PPMS.

Magnetic resonance outcomes. Proportion of patients with enhanced T1 lesions. At baseline, approximately 35% of patients in each treatment group had enhanced T1 lesions (figure 2, table 2). Whereas the proportion of patients with enhanced T1 lesions remained nearly unchanged from baseline to final evaluation in the placebo group, the proportion of cladribine-treated patients with enhanced T1 lesions decreased significantly, to 10% in the 0.7 mg/kg group ($p = 0.0080$) and 6% in the 2.1 mg/kg group ($p = 0.0009$). By final evaluation, there was a 70% reduction in the proportion of patients with enhanced T1 lesions in the cladribine 0.7 mg/kg group and an 83% reduction in this proportion in the cladribine 2.1 mg/kg group, compared with a reduction of 18% in the placebo group. The difference between the cladribine and placebo groups in the proportion of patients with enhanced T1 lesions was statistically significant at month 6 (see figure 2, table 2). It remained significant through month 18 for the 0.7 mg/kg dose and through month 24 for the 2.1 mg/kg dose (table 3).

Subgroup analysis of the proportion of patients with enhanced T1 lesions by pattern of disease showed no sig-

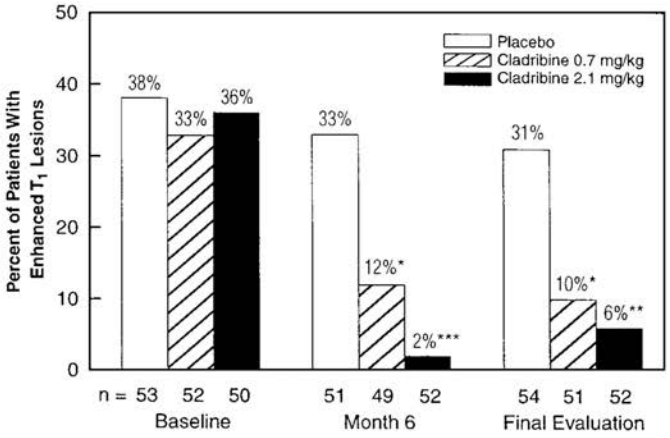

Figure 2. Proportion of patients with enhanced T1 lesions during the double-blind phase study. *p < *0.02 versus placebo.* **p < *0.001 versus placebo.* ***p < *0.0001 versus placebo.*

nificant difference among treatment groups in patients with PPMS (data not shown). In patients with SPMS, however, significantly smaller proportions of patients treated with either cladribine dose had enhanced T1 lesions at month 6 and the double-blind final evaluation, and those treated with 2.1 mg/kg maintained significant differences at follow-up months 18 and 24 (data not shown).

Examination of the relationship between the status of patients with and without enhanced T1 lesions at baseline and their status at final evaluation showed that for patients who presented without enhanced T1 lesions at baseline, new enhanced T1 lesions developed by final evaluation in 18% of placebo patients compared with 9% and 6%, respectively, of the low- and high-dose cladribine groups (NS). Moreover, for patients with enhanced T1 lesions present at baseline, the treatment effect on enhanced T1 lesions at final evaluation was significantly greater in patients receiving 0.7 mg/kg ($p < 0.02$) and 2.1 mg/kg ($p < 0.002$) cladribine than in the placebo patients; these differences in treatment effect between the placebo group

Table 3 *Summary of MRI outcomes during post–double-blind follow-up: all patients*

	Placebo	Cladribine 0.7 mg/kg		Cladribine 2.1 mg/kg	
MRI parameter	n (%) or mean (SD)	n (%) or mean (SD)	*p* Value	n (%) or mean (SD)	*p* Value
Enhanced T1 lesions					
Proportion of patients with lesions (%)[a–c]					
Baseline	14 (36%)	15 (32%)		16 (36%)	
Final evaluation	14 (36%)	5 (10%)	0.0079	2 (4%)	0.0002
Month 18	14 (36%)	5 (11%)	0.0089	1 (2%)	0.0001
Month 24	7 (24%)	4 (11%)	0.1965	0 (0%)	0.0014
Mean number of lesions (SD)[a,c,d]					
Baseline	0.64 (1.04)	1.72 (4.56)		1.09 (2.13)	
Final evaluation	0.62 (1.14)	0.13 (0.40)	0.004	0.04 (0.21)	<0.001
Month 18	0.62 (1.37)	0.20 (0.67)	0.011	0.07 (0.46)	<0.001
Month 24	1.17 (3.97)	0.26 (0.82)	0.182	0.0 (0.00)	0.001
Mean volume of lesions (μL)[a,c,d]					
Baseline	83.10 (160.33)	298.11 (826.49)		241.36 (816.41)	
Final evaluation	75.87 (126.94)	10.94 (39.99)	0.003	3.20 (15.10)	<0.001
Month 18	111.59 (351.47)	21.16 (90.58)	0.006	4.42 (28.97)	<0.001
Month 24	168.83 (708.80)	69.40 (236.50)	0.238	0.00 (0.00)	0.001
T2 lesions					
Mean lesion volume (mL) (SD)[a,c,d]					
Baseline	10.42 (8.80)	13.28 (12.49)		10.34 (8.81)	
Final evaluation	10.47 (8.71)	12.87 (12.06)	0.395	10.08 (8.87)	0.825
Month 18	10.50 (8.75)	13.22 (12.21)	0.379	9.91 (8.29)	0.769
Month 24	10.75 (9.55)	12.41 (12.95)	0.839	10.36 (8.83)	0.945
Percent change from baseline to Month 24[c,e]					
Mean (SD)	3.74 (15.38)	1.02 (23.16)		−4.22 (17.55)	

[a] Includes patients with both baseline and final evaluations.
[b] Fisher's exact test (two-sided significance).
[c] The final evaluation is the last evaluation of the double-blind phase.
[d] Based on Wilcoxon's (Mann-Whitney) rank sum test.
[e] Positive change indicates disease progression.

and cladribine groups were statistically significant at month 6.

Volume and number of enhanced T1 lesions. The cladribine groups had approximately 90% reductions in the mean number of enhanced T1 lesions at month 6 and maintained 92% reductions through final evaluation, compared with 33% and 50% reductions in the placebo group at month 6 and final evaluation, respectively (see table 2). The differences in the numbers of these lesions at the final evaluation between the placebo and cladribine 0.7 mg/kg groups ($p = 0.005$) and the placebo and cladribine 2.1 mg/kg groups ($p = 0.001$) were statistically significant, as were the differences at month 6. Compared with a 3% reduction in the mean number of enhanced T1 lesions in the placebo group at month 18 and a 77% increase at month 24, the cladribine groups maintained a 91% reduction at month 18 ($p < 0.001$) and month 24 ($p = 0.005$, see table 3).

The mean volume of enhanced T1 lesions also decreased from baseline in all three treatment groups during double-blind therapy, with greater reductions observed in the two cladribine groups (96% and 97%, respectively, for the low- and high-dose groups) compared with the placebo group (45%; see table 2). Differences between placebo and cladribine treatments in enhanced T1 lesion volume were statistically significant at each timepoint after baseline, with >90% reduction in both cladribine treatment groups at month 6. Compared with 34% and 70% increases in the volume of enhanced T1 lesions in the placebo group at months 18 and 24, respectively, patients receiving cladribine had a 95% reduction in volume at month 18 ($p < 0.001$) and an 87% reduction at month 24 ($p = 0.007$, see table 3).

Subgroup analysis of the volume and number of enhanced T1 lesions by pattern of disease and post-double-blind follow-up data are consistent with the observations on proportions of patients having such lesions and support the finding that the effect of cladribine on suppression of enhanced T1 lesions is greater in patients with SPMS and is sustained for up to 24 months, particularly at the 2.1 mg/kg dose.

Volume of T2 lesions. Mean baseline T2 lesion volumes were generally comparable across all treatment groups. During the double-blind phase, both cladribine groups had a slight decrease in mean T2 lesion volume from baseline to final evaluation (−0.39 mL for the cladribine 0.7 mg/kg group and −0.20 mL for the cladribine 2.1 mg/kg group; the placebo group showed a mean increase of 0.41 mL) (see table 2). The change from baseline to final evaluation between the placebo group and the cladribine 2.1 mg/kg group was statistically significant ($p = 0.040$), indicating that lesion load did not accumulate as rapidly in the high-dose cladribine group.

In the placebo group, there was a median percent increase of 1.53% in T2 lesion volume from baseline to final evaluation (see table 2). Cladribine-treated patients, however, had a small, dose-dependent, median percent decrease in T2 lesion volume during the double-blind phase of the study, suggesting a stabilization of T2 lesion accumulation by the end of 1 year following the start of treatment (figure 3). The difference in median percent change in T2 lesion volume for the cladribine 2.1 mg/kg group was

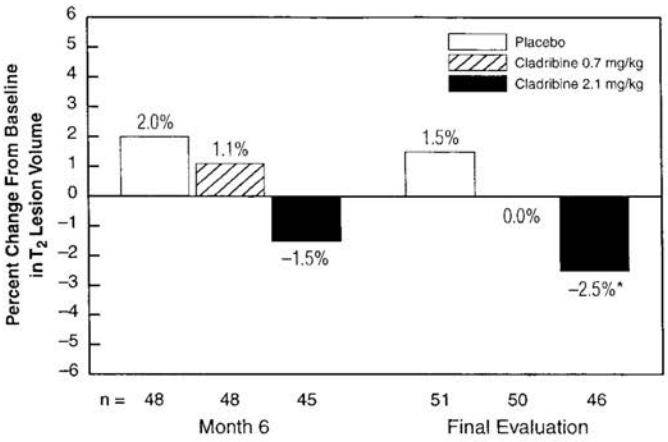

Figure 3. Change in T2 lesion volume over time during the double-blind phase of the study. *p = *0.029 versus placebo.*

significantly different from that for placebo treatment ($p = 0.029$).

Among patients with available data during the second year of follow-up, the mean percent change in T2 lesion volume remained negative at −4.2% in patients treated with 2.1 mg/kg cladribine, whereas the placebo group continued to show an increase of 3.7% and the 0.7 mg/kg group showed a slight increase of 1.0% (see table 3). Subgroup analysis showed that the treatment effect of cladribine on median percent change in T2 lesion volume was significant over 24 months of follow-up in patients with SPMS but not in those with PPMS (data not shown). Moreover, the decrease in T2 lesion volume, which appeared to be dose related in the overall study analysis, was independent of dose in patients with SPMS.

Safety evaluation. All 159 patients were included in the safety analyses. Most patients within each treatment group received the maximum assigned total cladribine doses. Cladribine was generally well tolerated, and 97% of patients completed the 12-month double-blind phase of the study. There were no drop-outs due to adverse events.

Adverse events. A majority of reported adverse events occurred with comparable frequency in patients who received placebo and patients treated with cladribine. Most of the adverse events in all three treatment groups were mild or moderate in severity, not treatment limiting, and were judged by the investigator to be unlikely to be related to study drug therapy. Many of the frequently reported adverse events, such as pain, urinary tract infection, and injury, were often related to the underlying disease, and the various application site disorders were related to subcutaneous injection of the study medication.

The most common treatment-emergent adverse events (reported for ≥10% of patients in any treatment group), whose frequency was at least 5% higher among patients in one or both cladribine groups relative to the placebo group, are listed in table 4. Muscle weakness, hypertonia, purpura, rhinitis, and ataxia occurred more frequently among cladribine-treated patients than in the placebo group. Injection site pain, injury, dizziness, and tremor were reported more frequently in the placebo group than in cladribine-treated patients. Upper respiratory tract infection, pharyngitis, back pain, arthralgia, and skin disorder were more common in patients in the cladribine

Table 4 *Treatment-emergent adverse events seen more frequently in cladribine-treated patients**

Preferred term	Placebo, n = 54	Cladribine 0.7 mg/kg, n = 53	Cladribine 2.1 mg/kg, n = 52
Upper respiratory tract infection	16 (30)	13 (25)	23 (44)
Muscle weakness	3 (6)	10 (19)	11 (21)
Purpura	5 (9)	8 (15)	13 (25)
Injection site reaction	9 (17)	7 (13)	13 (25)
Hypertonia	6 (11)	9 (17)	10 (19)
Back pain	7 (13)	5 (9)	11 (21)
Urinary tract infection	6 (11)	10 (19)	6 (12)
Depression	9 (17)	12 (23)	4 (8)
Arthralgia	4 (7)	4 (8)	7 (13)
Rhinitis	2 (4)	5 (9)	5 (10)
Ataxia	2 (4)	4 (8)	5 (10)
Pharyngitis	2 (4)	1 (2)	8 (15)

Values are n (%).

* Adverse events reported by ≥10% of the patients in any one of the three treatment groups and ≥5% more patients in a cladribine group than in the placebo group.

2.1 mg/kg group than in those receiving cladribine 0.7 mg/kg or placebo.

Among the less common but clinically important treatment-emergent adverse events, the incidence of infections not usually seen in the MS population was similar in the three treatment groups. One patient in each treatment group experienced herpes zoster infection of marked severity; in two of these patients, one receiving placebo and the other 0.7 mg/kg cladribine, the infection contributed to discontinuation of the study drug, and all three cases resolved with antiviral treatment. Herpes simplex infection occurred in 3 (6%) placebo-treated patients and in 1 (2%) patient in the cladribine 0.7 mg/kg group.

Clinical laboratory analytes. *Hematologic changes.* At the final evaluation of the double-blind period, dose-related decreases in mean leukocyte count, absolute lymphocyte count, absolute neutrophil count, absolute monocyte count, platelet count, hemoglobin, and hematocrit were observed in cladribine-treated patients, compared with small increases or no change in the mean values of these analytes in the placebo group. Consistent with the expected pharmacologic activity of cladribine, the largest observed effect was a suppression in lymphocyte count. The mean lymphocyte count was suppressed at both dosage levels of cladribine from the first cycle of treatment throughout the double-blind observation phase, and remained below the normal range for this analyte over time in the 2.1 mg/kg group (figure 4). The observed decreases in the other analytes were modest, and the mean values were within the normal range at the final visit. Two patients (one receiving placebo and the other high-dose cladribine) had short-lived thrombocytopenia (platelet counts ≤ 100×10^9/L), and one patient in the cladribine 2.1 mg/kg group had a single low neutrophil count (960/μL).

Lymphocyte subset analyses showed cladribine treatment to be associated with dose-dependent decreases in

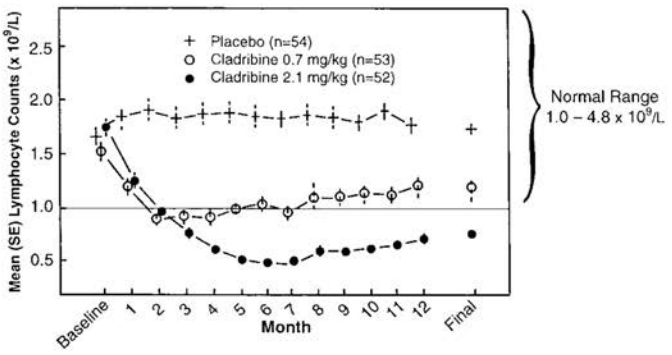

Figure 4. Change in mean lymphocyte count over time during the double-blind phase of the study.

mean levels of $CD4^+$, $CD3^+$, $CD8^+$, and to a lesser degree, $CD19^+$ lymphocytes. More patients in the 2.1 mg/kg group experienced $CD4^+$ counts ≤ 200/μL (n = 31) than did those in the 0.7 mg/kg (n = 5) or placebo (n = 1) groups; two patients in the high-dose group had at least one $CD4^+$ count ≤ 50/μL. In addition, there was a dose-dependent decrease in the mean $CD4^+/CD8^+$ ratio among cladribine-treated patients compared with a small increase among placebo-treated patients. Although both $CD4^+$ and $CD8^+$ lymphocyte counts showed a dose-related suppression among cladribine-treated patients, the observed decrease in the $CD4^+/CD8^+$ ratio indicated a more pronounced effect on the $CD4^+$ subset. Subset analysis also revealed a modest and transient dose-dependent increase in the mean percentage of $CD16^+$ plus $CD56^+$ lymphocytes. The relatively minor, transient effect on $CD19^+$ lymphocytes and the effect on $CD16^+$ plus $CD56^+$ lymphocytes may explain the relatively low number of serious infections in the presence of significant overall lymphocytopenia.

Serum chemistry. Examination of mean changes from baseline to final evaluation during the double-blind phase revealed no treatment-related effects on hepatic or renal function tests or other serum chemistries.

Physical findings. Mean changes from baseline values for vital signs, body weight, physical findings, and ECG were small and clinically insignificant.

Discussion. Using EDSS scores as an outcome measure, no significant treatment effects were found for cladribine in this double-blind study of patients with progressive MS. The lack of overall treatment difference in this study is likely due to the majority of patients having relatively high EDSS scores at baseline (median score for all three treatment groups, 6.0) and the placebo group having only a modest increase from baseline in mean EDSS score. Multivariate predictive models of short-term and long-term worsening on the EDSS and meta-analysis of placebo-treated control groups in progressive MS have shown that the spectrum of disability is bimodal, with one peak at EDSS 1 to 3 and another at 6.[32] Patients with a baseline EDSS score of 3.0 to 5.0 are much more likely to deteriorate by 1 full point on the EDSS in a shorter period of time than are those with a baseline score ≥ 6.0.[33,34]

The statistical sizing and duration of the double-blind phase of this study were based on the assump-

tion that placebo-treated patients with progressive MS would show a greater degree of disease progression over the course of 12 months and did not anticipate enrollment of mainly patients with more severe disability. The trial was underpowered for the patient population enrolled. In addition, patients with PPMS may be more resistant to therapy than those with SPMS, and approximately one third of the patients enrolled in this study had PPMS. Subgroup analysis by disease pattern suggested stabilization of disability in cladribine-treated patients with SPMS at final evaluation but not in those with PPMS. Long-term follow-up through month 24 showed a trend toward a beneficial cladribine effect in the SPMS subgroup at both the 0.7 and 2.1 mg/kg doses.

Because clinical efficacy was not shown in this trial, it is necessary to scrutinize the Scripps study for type I errors (false positives). Sources of concern in the Scripps trial[25] include the replacement of cladribine dropouts in a small crossover trial. An intent-to-treat analysis, which would have included data from these patients, is mentioned but not reported in detail. The disability scores upon which efficacy was determined were not "confirmed" by a definition of sustained worsening over the standard 3- to 6-month periods used in other trials. The use of means of ordinal scores (e.g., the Kurtzke scale) as an outcome measure is problematic. In the second year of the study, 5/24 patients destined to receive placebo in the crossover limb actually received one dose of cladribine. Rapid worsening of the placebo group presaged the ultimate failure of the trial's reproducibility. This type of placebo-group worsening has been the Achilles heel of many previous studies. The late (month 27 to 30) worsening of patients who received cladribine initially, although perhaps contaminated by small numbers and examiner unblinding (which should have mitigated the effect), suggested that the early treatment effect was not durable.[26]

The MRI findings, however, were more compelling. Gadolinium-enhanced T1 lesions represent areas of breakdown in the blood–brain barrier and are generally believed to be sites of new inflammation that probably precede symptoms and other MRI signs in MS.[35] Gadolinium-enhancing lesions were virtually eliminated by treatment with cladribine. Both the 0.7 mg/kg and 2.1 mg/kg doses were significantly superior to placebo with respect to the proportion of patients having detectable enhanced T1 lesions as well as to the mean volume and number of such lesions at 6 months and final evaluation. Moreover, statistically significant differences were maintained through month 18 for the 0.7 mg/kg dose and through month 24 for the 2.1 mg/kg dose. These MRI outcomes compare favorably with those in a recently published 2-year study of interferon β-1b in the treatment of patients with SPMS (mean baseline EDSS score, 5.1 ± 1.1),[14] and are supported by similar observations from two previous studies with cladribine treatment in patients with SPMS (median EDSS score, 4.0)[25,26] and in patients with RRMS (median EDSS score, 3.5).[36]

Although it is conceivable that events related to progression are different from those involved with the inflammation identified by gadolinium enhancement, the MRI changes in this study were robust. Longitudinal natural history studies in MS patients suggest that clinical and radiologic worsening over the short term can be predicted by gadolinium enhancement and by new T2 lesions.[37] However, enhancement does not appear to predict the development of long-term disability in MS, at least in studies of 2 years' duration.[22]

Cladribine doses of 0.7 mg/kg and 2.1 mg/kg were well tolerated. The most common adverse events were related to the patients' underlying disease or to SC administration of the study drug. They were mild or moderate in severity, not treatment limiting, and were judged by the investigator to be unrelated to study drug therapy. There were no systemic constitutional signs and symptoms that would have led to unblinding. Cells of most hematologic lineages showed modest dose-related suppression following cladribine treatment but means were within the normal range; this is an expected consequence of the selective lymphocytotoxic effects of the drug. A more marked, long-lasting, dose-related lymphocyte count reduction confirmed the pharmacologic activity of cladribine in this study. This has persisted beyond 2 years in several patients. Herpes infections occurred rarely, with similar frequencies in the three treatment groups, and resolved with appropriate medical care. There were no serious infections in this group of patients; the risk of potentially serious infections not commonly encountered in patients with MS appears to be higher in patients with SPMS receiving cladribine at a dose of 2.8 mg/kg.[25,26]

Although serious neurologic, hepatic, and renal adverse events have been observed in cancer patients receiving cladribine at doses considerably higher than those administered to patients with MS,[24,38] no serious adverse events could be attributed to cladribine treatment in this study. There were no treatment-related deaths, no suicides or suicide attempts, and the incidence of depression was considerably lower in patients treated with 2.1 mg/kg than in the other two groups.

The cladribine doses used in the current study were chosen to reduce the hematopoietic effects of the drug reported in the previous trial, in which a total dose of 2.8 mg/kg was administered.[25,26] The high dose in the current study (2.1 mg/kg) suppressed the mean lymphocyte count by 60%, compared with 70% in the previous study. The intensity of the dosing schedule differed in the two trials (0.07 mg/kg/day versus 0.1 mg/kg/day; 0.35 mg/kg/5-day cycle versus 0.7 mg/kg/7-day cycle), which may have contributed to the improved tolerability and lower incidence of infections in this study.

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Appendix 1

The Cladribine Clinical Study Group comprises the following participating research centers, principal investigators (in italics), and investigative teams: University Hospital, London, Ontario, Canada—*George P. A. Rice, MD,* George Ebers, MD, Kang Howson-Jan, MD, M. Vandervoort, RN, L. Froste, RN, W. Koopman; Oregon Health Sciences University, Portland, OR—*Dennis N. Bourdette, MD,* James J. Cereghino, MD, Michele K. Mass, MD, Joseph Quinn, MD, Gerald M. Segal, MD, Ruth H. Whitham, MD; Yale University School of Medicine, New Haven, CT—*Joseph B. Guarnaccia, MD,* Brian Smith, MD, Jonathan M. Goldstein, MD, Henry M. Rinder, MD; University of Medicine and Dentistry of New Jersey, Newark, NJ—*Stuart D. Cook, MD,* Shalini Bansil, MD, Mary Ann Picone, MD; Allegheny University of the Health Sciences, Philadelphia, PA—*Fred D. Lublin, MD;* Thomas Jefferson University, Philadelphia, PA—*Robert L. Knobler, MD;* University of British Columbia, Vancouver, Canada—*Joel Oger, MD,* Stanley A. Hashimoto, MD, Donald W. Paty, MD; The R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ—James Baldassarre, MD, Liang Xiu, PhD.

The Cladribine MRI Study Group consists of the following investigators: Neuroimaging Research Unit, Dept of Neuroscience, Scientific institute Ospedale San Raffaele, University of Milan, Italy—*Massimo Filippi, MD,* Giovanna Mastronardo, MD, Marco Rovaris, MD; Clinical Trials Unit, Dept of Neuroscience, Scientific Institute Ospedale San Raffaele, University of Milan, Italy—*Giancarlo Comi, MD.*

The Independent Safety Monitoring Board was composed of N. Fishman, MD, University of Pennsylvania, Philadelphia; R. Hemdon, MD, Department of Veterans Affairs, Jackson, MS; S. van den Noort, MD, University of California, Irvine; K. Rai, MD, Long Island Jewish Medical Center, New Hyde Park, NY; N. Temkin, MD, Harborview Medical Center, Seattle, WA; W. Tourtellotte, MD, PhD, Veterans Affairs Medical Center, Los Angeles, CA.

Appendix 2

Hematologic dosing criteria

1. Platelet count:
   $\geq 200 \times 10^9$/L *or*
   if $150–200 \times 10^9$/L, not <50% of previous count *or*
   if $125–150 \times 10^9$/L, not <80% of previous count
2. Absolute neutrophil count $> 1.0 \times 10^9$/L
3. Hemoglobin:
   no decline >1.5 g/dL from previous monthly value *or*
   no decline >3 g/dL from baseline value

References

1. Anderson DW, Ellenberg JH, Leventhal CM, Reingold SC, Rodriguez M, Silberberg DH. Revised estimate of the prevalence of multiple sclerosis in the United States. Ann Neurol 1992;31:333–336.
2. Weinshenker BG. Natural history of multiple sclerosis. Ann Neurol 1994;36:S6–S11.
3. Goodkin DE. Interferon-β therapy for multiple sclerosis. Lancet 1998;352:1486–1487.
4. Jacobs LD, Cookfair DL, Rudick RA, et al. A phase III trial of intramuscular recombinant interferon beta as treatment for exacerbating-remitting multiple sclerosis: design and conduct of study and baseline characteristics of patients. Multiple Sclerosis Collaborative Research Group (MSCRG). Mult Scler 1995;1:118–135.
5. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996;39:285–294.
6. Rudick RA, Goodkin DE, Jacobs LD, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Neurology 1997;49:358–363.
7. Simon JH, Jacobs LD, Campion M, et al. Magnetic resonance studies of intramuscular interferon β-1a for relapsing multiple sclerosis. Ann Neurol 1998;43:79–87.
8. Fieschi C, Pozzilli C, Bastianello S, et al. Human recombinant interferon beta in the treatment of relapsing-remitting multiple sclerosis: preliminary observations. Mult Scler 1995; 1(suppl 1):S28–S31.
9. Pozzilli C, Bastianello S, Koudriavtseva T, et al. Magnetic resonance imaging changes with recombinant human interferon-β-1a: a short term study in relapsing-remitting multiple sclerosis. J Neurol Neurosurg Psychiatry 1996;61:251–258.
10. Paty DW, Blumhardt LD, on behalf of the transitional PRISMS Study Group. High-dose subcutaneous interferon β-1a is efficacious in transitional multiple sclerosis, a group at high risk for progression in disability. Ann Neurol 1998;44: 503. Abstract W240.
11. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993;43:655–661.
12. Paty DW, Li DKB, the UBC MS/MRI Study Group, the IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993;43:662–667.
13. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. Neurology 1995;45:1277–1285.
14. European Study Group on Interferon β-1b in Secondary Progressive MS. Placebo-controlled multicentre randomised trial of interferon β-1b in treatment of secondary progressive multiple sclerosis. Lancet 1998;352:1491–1497.
15. Miller DH, Albert PS, Barkhof F, et al. Guidelines for the use of magnetic resonance techniques in monitoring the treatment of multiple sclerosis. Ann Neurol 1996;39:6–16.
16. McFarland HF, Frank JA, Albert PS, et al. Using gadolinium-enhanced magnetic resonance imaging lesions to monitor disease activity in multiple sclerosis. Ann Neurol 1992;32:758–766.
17. Smith ME, Stone LA, Albert PS, et al. Clinical worsening in multiple sclerosis is associated with increased frequency and area of gadopentetate dimeglumine-enhancing magnetic resonance imaging lesions. Ann Neurol 1993;33:480–489.
18. Stone LA, Smith ME, Albert PS, et al. Blood–brain barrier disruption on contrast-enhanced MRI in patients with mild relapsing-remitting multiple sclerosis: relationship to course, gender, and age. Neurology 1995;45:1122–1126.
19. Koudriavtseva T, Thompson AJ, Pozzilli C, et al. Role of a baseline scan in predicting clinical and MRI activity of relapsing-remitting MS patients. J Neuroimmunol 1995; 61(suppl 1):41. Abstract.
20. Filippi M, Horsfield MA, Tofts PS, Barkhof F, Thompson AJ, Miller DH. Quantitative assessment of MRI lesion load in monitoring the evolution of multiple sclerosis. Brain 1995;118: 1601–1612.
21. Filippi M, Horsfield MA, Morrissey SP, et al. Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. Neurology 1994; 44:635–641.
22. Kappos L, Moere EW, Schoetzau A, et al. Predictive value of magnetic resonance imaging for relapse rate and changes in disability or impairment in multiple sclerosis: a meta-analysis. Lancet 1999;353:964–968.
23. Evans AC, Frank JA, Antel J, Miller DH. The role of MRI in clinical trials of multiple sclerosis: comparison of image processing techniques. Ann Neurol 1997;41:125–132.
24. Beutler E. Cladribine (2-chlorodeoxyadenosine). Lancet 1992; 340:952–956.
25. Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J, Beutler E. Cladribine in treatment of chronic progressive multiple sclerosis. Lancet 1994;344:9–13.
26. Beutler E, Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J. The treatment of chronic progressive multiple sclerosis with cladribine. Proc Natl Acad Sci USA 1996;93:1716–1720.
27. Schumacher GA, Beebe G, Kibler RF, et al. Problems of experimental trials of therapy in multiple sclerosis: report by the

panel on the evaluation of experimental trials of therapy in multiple sclerosis. Ann NY Acad Sci 1965;122:552–568.
28. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227–231.
29. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). Neurology 1983;33:1444–1452.
30. Barkhof F, Filippi M, van Waesberghe JH, et al. Improving interobserver variation in reporting gadolinium-enhanced MRI lesions in multiple sclerosis. Neurology 1997;49:1682–1688.
31. Filippi M, Gawne-Cain ML, Gasperini C, et al. Effect of training and different measurement strategies on the reproducibility of brain MRI lesion load measurements in multiple sclerosis. Neurology 1998;50:238–244.
32. 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;112:133–146.
33. Weinshenker BG, Issa M, Baskerville J. Long-term, short-term outcome of multiple sclerosis: a 3-year follow-up study. Arch Neurol 1996;53:353–358.
34. Weinshenker BG, Issa M, Baskerville J. Meta-analysis of the placebo-treated groups in clinical trials of progressive MS. Neurology 1996;46:1613–1619.
35. Kermode AG, Thompson AJ, Tofts P, et al. Breakdown of the blood-brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis. Brain 1990;113:1477–1489.
36. Sipe JC, Romine JS, Koziol J, Zyroff J, McMillan R, Beutler E. Cladribine improves relapsing-remitting MS: a double blind, placebo controlled study. Neurology 1997;48(suppl 2):A340. Abstract S345.003.
37. Molyneux PD, Filippi M, Barkhof F, et al. Correlations between monthly enhanced MRI lesion rate and changes in T2 lesion volume in multiple sclerosis. Ann Neurol 1998;43:332–339.
38. Beutler E, Piro LD, Savan A. 2-Chlorodeoxyadenosine (2-CdA): a potent chemotherapeutic and immunosuppressive nucleoside. Leuk Lymphoma 1991;5:1–8.

A Wallerian degeneration pattern in patients at risk for MS

J.H. Simon, MD, PhD; R.P. Kinkel, MD; L. Jacobs, MD; L. Bub, MD; and N. Simonian, MD

Article abstract—*Background:* Demyelination alone may not explain the progressive disability that frequently develops in MS. An alternative explanation for irreversible disability assumes a contribution from axonal injury or loss. In theory, axonal injury may occur in the focal areas characterized by early inflammation, or can be more distant, as in Wallerian degeneration. However, Wallerian degeneration is thought of as a rare or a late finding in MS. *Methods:* Studies showing a classic Wallerian degeneration pattern in the corticospinal tract were selected from a review of MR studies from patients enrolled in a longitudinal treatment trial. Entry was based on first occurrence of an isolated neurologic syndrome consistent with MS and a positive MRI. *Results:* This report is based on five cases followed longitudinally who showed development of a classic T2-hyperintense lesion along the ipsilateral corticospinal tract, subsequent to an initial inciting event located in the white matter located in the superior aspect of the corona radiata. Lesions were evident as T2-hyperintensity persisting throughout the 12 to 18 months of observation. *Conclusions:* This series suggests that Wallerian degeneration, implying axonal injury, may occur as a sequela of acute demyelinating lesions in patients presenting with their first symptoms suggestive of MS. This can produce a component of the increasing burden of T2-hyperintense lesions temporally and spatially dissociated from inflammatory or demyelinating activity. Further studies are required to determine if Wallerian degeneration is an important factor contributing to disability progression in MS. **Key words:** Wallerian degeneration—MS.

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MS is understood to be a predominantly inflammatory and demyelinating disease with glial proliferation that is relatively sparing of axons. When described in MS, axonal injury has generally been considered a finding of late stages of disease, or as a consequence of relatively severe, but rare lesions.[1-3] As demyelination alone may not account for progressive disability in MS, interest has been focused re-

From the Neuroradiology/MRI Department (Drs. Simon and Bub), University of Colorado Health Sciences Center, Denver; Mellen Center for MS Treatment and Research (Dr. Kinkel), Cleveland Clinic Foundation, Cleveland, OH; Department of Neurology (Dr. Jacobs), SUNY Buffalo, Buffalo General Hospital, NY; and Biogen Inc. (Dr. Simonian), Cambridge, MA.

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Address correspondence and reprint requests to Dr. Jack H. Simon, University of Colorado Health Sciences Center, 4200 E Ninth Avenue Box A034, Neuroradiology/MRI, Denver, CO 80262; e-mail: jack.simon@uchsc.edu

