ORIGINAL ARTICLE

A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis

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ABSTRACT

BACKGROUND

Cladribine provides immunomodulation through selective targeting of lymphocyte subtypes. We report the results of a 96-week phase 3 trial of a short-course oral tablet therapy in patients with relapsing–remitting multiple sclerosis.

METHODS

We randomly assigned 1326 patients in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year). The primary end point was the rate of relapse at 96 weeks.

RESULTS

Among patients who received cladribine tablets (either 3.5 mg or 5.25 mg per kilogram), there was a significantly lower annualized rate of relapse than in the placebo group (0.14 and 0.15, respectively, vs. 0.33; P<0.001 for both comparisons), a higher relapse-free rate (79.7% and 78.9%, respectively, vs. 60.9%; P<0.001 for both comparisons), a lower risk of 3-month sustained progression of disability (hazard ratio for the 3.5-mg group, 0.67; 95% confidence interval [CI], 0.48 to 0.93; P=0.02; and hazard ratio for the 5.25-mg group, 0.69; 95% CI, 0.49 to 0.96; P=0.03), and significant reductions in the brain lesion count on magnetic resonance imaging (MRI) (P<0.001 for all comparisons). Adverse events that were more frequent in the cladribine groups included lymphocytopenia (21.6% in the 3.5-mg group and 31.5% in the 5.25-mg group, vs. 1.8%) and herpes zoster (8 patients and 12 patients, respectively, vs. no patients).

CONCLUSIONS

Treatment with cladribine tablets significantly reduced relapse rates, the risk of disability progression, and MRI measures of disease activity at 96 weeks. The benefits need to be weighed against the risks. (ClinicalTrials.gov number, NCT00213135.)

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Multiple sclerosis is a chronic and debilitating autoimmune disorder of the central nervous system, in which T and B cells are believed to play a major pathophysiological role.[1-3] Treatment benefits and disease modification can be obtained with the currently approved parenteral immunomodulatory and immunosuppressant therapies: interferon beta, glatiramer acetate, mitoxantrone, and natalizumab. However, treatment responses are often less than complete, and concern regarding safety and side-effect profiles may limit the general use of these drugs. The need for parenteral administration may present relative or absolute barriers to access, limiting treatment adherence and long-term outcomes.[4]

Intracellular accumulation of the active metabolite of cladribine, 2-chlorodeoxyadenosine triphosphate, results in the disruption of cellular metabolism, the inhibition of DNA synthesis and repair, and subsequent apoptosis.[5] Cladribine preferentially affects lymphocytes because these cells have a relatively high ratio of deoxycytidine kinase to 5′-nucleotidase and are dependent on adenosine deaminase activity to maintain the equilibrium of cellular concentrations of triphosphorylated nucleotides. The accumulation of the cladribine nucleotide produces rapid and sustained reductions in CD4+ and CD8+ cells and rapid, though more transient, effects on CD19+ B cells, with relative sparing of other immune cells.[5-8] Cladribine also has been shown to cause a reduction in the levels of proinflammatory cytokines and serum and cerebrospinal fluid chemokines, in adhesion molecule expression, and in mononuclear-cell migration.[5,9-13]

In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) study, we investigated the efficacy and safety of cladribine in a 96-week, phase 3, double-blind, placebo-controlled, multicenter trial involving patients with relapsing–remitting multiple sclerosis. The two doses of cladribine that we evaluated were based on the results of previous clinical studies that used a parenteral formulation of the drug in various regimens.[7,14-16] In order to provide an extended interim hematopoietic recovery period before subsequent retreatment, we administered cladribine in short courses within separate 48-week periods rather than administering the aggregate treatment as six to eight consecutive monthly courses.

Methods

Patients

From April 20, 2005, to January 18, 2007, we recruited patients from 155 clinical centers in 32 countries (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients were eligible if they had received a diagnosis of relapsing–remitting multiple sclerosis (according to the McDonald criteria),[17] had lesions consistent with multiple sclerosis on magnetic resonance imaging (MRI) (according to the Fazekas criteria),[18] had had at least one relapse within 12 months before study entry, and had a score of no more than 5.5 on the Kurtzke Expanded Disability Status Scale (EDSS, which ranges from 0 to 10, with higher scores indicating a greater degree of disability).[19]

Patients were excluded from the study if two or more previous disease-modifying therapies had failed or if they had received immunosuppressive therapy at any time before study entry or cytokine-based therapy, intravenous immune globulin therapy, or plasmapheresis within 3 months before study entry. Patients were also excluded if they had abnormal results on hematologic testing (a platelet or neutrophil count below the lower limit of the normal range or a leukocyte count of half the lower limit of the normal range) within 28 days before study entry, had a disorder that could compromise immune function (including systemic disease or infection with the human immunodeficiency virus or human T-cell lymphotropic virus), or had had a relapse within 28 days before study entry. For any patient who had received a disease-modifying drug for multiple sclerosis, a washout period of at least 3 months before study entry was required.

Study Design

Eligible patients were assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine over 96 weeks (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo. Randomization was performed with the use of a central system and a computer-gen-

10.1056/NEJMoa0902533 NEJM.org

erated treatment randomization code, with dynamic allocation by site in permuted blocks of six. The study drugs were administered orally as short courses, each consisting of one or two 10-mg cladribine tablets or matching placebo given once daily for the first 4 or 5 days of a 28-day period.

In the first 48-week treatment period, patients received either two courses of cladribine, followed by two courses of placebo (in the 3.5-mg group); four courses of cladribine (in the 5.25-mg group); or four courses of placebo (in the placebo group), starting at day 1 and at weeks 5, 9, and 13 (8 to 20 days of treatment). In the second 48-week period, both cladribine groups received two courses of cladribine, and the placebo group received two courses of placebo, starting at weeks 48 and 52 (8 to 10 days of treatment) (Fig. 1 in the Supplementary Appendix). After week 24, rescue therapy with subcutaneous interferon beta-1a (at a dose of 44 μg three times per week) was available if a patient had more than one relapse or a sustained increase in the EDSS score.

The study was conducted in accordance with relevant clinical guidelines (see the Supplementary Appendix). All patients provided written informed consent.

STUDY OVERSIGHT

The protocol was reviewed and approved by the local review board or ethics committee at each study center. An independent data and safety monitoring board reviewed the study conduct and all safety data. Data were gathered by an independent commercial research organization and analyzed by the sponsor (Merck Serono) in accordance with the statistical plan. MRI data were analyzed by an independent commercial research organization at a central reading center. The authors were involved in all stages of development and finalization of the manuscript and were assisted by an independent medical-writing-services agency paid by Merck Serono. The first draft of the manuscript was cowritten by the lead academic author and a representative of the sponsor, with the medical-writing-services agency providing support as directed. The authors vouch for the completeness and accuracy of the data and analyses.

STUDY PROCEDURES

To maintain the double-blind nature of the study, all patients within a weight range received the same number of tablets (cladribine or matched placebo). In addition, at each study site, a treating physician reviewed clinical laboratory results and assessed treatment-emergent adverse events and safety information, and an independent evaluating physician who was unaware of study-group assignments performed neurologic examinations and determined whether a clinical event fulfilled criteria consistent with a relapse. Evaluators at a central neuroradiology center assessed MRI evaluations in a blinded fashion.

Neurologic examinations included the EDSS evaluation,[19] which was conducted at the prestudy evaluation and at day 1 and at weeks 13, 24, 36, 48, 60, 72, 84, and 96. MRI scans were obtained at the prestudy evaluation and at weeks 24, 48, and 96. Clinical laboratory tests, including chemical and hematologic analyses and urinalysis, were performed by a central laboratory at frequent intervals during the 96-week study (for details, see the Supplementary Appendix). For suspected relapses occurring between study visits, patients were required to attend the study site within 7 days after the onset of neurologic symptoms for objective assessment by the evaluating physician in a blinded fashion. Relapses could be treated with intravenous corticosteroids at the discretion of the treating physician.

PRIMARY AND SECONDARY END POINTS

The primary end point was the rate of relapse at 96 weeks. A relapse was defined as an increase of 2 points in at least one functional system of the EDSS or an increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement.

Key clinical secondary efficacy end points were the proportion of patients who were relapse-free and the time to sustained progression of disability, which was defined as the time to a sustained increase (for at least 3 months) of at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score was 0. Additional clinical efficacy end points included the time to the first relapse and the proportion of patients receiving rescue therapy with interferon beta-1a. Secondary MRI end points were the mean number of lesions per patient per scan at 96 weeks for gadolinium-enhancing T_1-weighted lesions, active T_2-weighted lesions, and combined

unique lesions, which were defined as new gadolinium-enhancing T_1-weighted lesions or new nonenhancing or enlarging T_2-weighted lesions (without double-counting).

The safety assessment included a review of the incidence of treatment-emergent adverse events in each study group, physical examination, and laboratory measurements. A strict protocol was established for the management of hematologic events (see the Supplementary Appendix).

STATISTICAL ANALYSIS

We determined that 1290 patients (approximately 430 in each group) were required to provide a power of 90% to detect a clinically meaningful relative reduction of 25% in the relapse rate in the cladribine groups, as compared with the placebo group, at 96 weeks (the primary end point). This was calculated with the use of a two-sided t-test on the assumption that a mean number of 2.1 relapses would occur in the placebo group, that the standard deviation for the number of relapses in each group would be 2.02, that the proportion of patients who could not be evaluated would be 10%, and that the two-sided type I error rate for the comparison between each cladribine group and the placebo group would be 2.5%.

The intention-to-treat population included all patients who underwent randomization, and the safety population included all patients who received at least one dose of a study drug and for whom follow-up safety data were available. The primary efficacy measurement was analyzed with the use of a Poisson regression model including effects for treatment and region and the log of time in the study as the offset variable. The study groups were compared by means of an approximate chi-square test on the basis of Wald statistics and Hochberg's step-up method for multiple comparisons to protect the type I error.

For patients who received rescue therapy, the primary and secondary efficacy analyses included the prerescue data and imputed data from the time of rescue onward, according to prespecified methods in the statistical analysis plan. For the primary end point, imputed data were derived only from patients in the placebo group.

In the analysis of secondary end points, the proportions of patients who were relapse-free and progression-free were analyzed with the use of a logistic-regression model that included study-group and region effects, and odds ratio and 95% confidence intervals were estimated for each study group. The three study groups were compared with the use of an approximate chi-square test on the basis of Wald statistics. The time to the first relapse and the time to a 3-month sustained change in the EDSS score were analyzed with the use of a Cox proportional-hazards model that included study-group and region effects, and the hazard ratio for the time to the first relapse and the time to a 3-month sustained change in the EDSS score in each group and associated 95% confidence intervals were estimated. Kaplan–Meier plots of the time to the first relapse and the time to a 3-month sustained change in the EDSS score were also generated.

Secondary end points that were related to lesion counts on MRI were analyzed with the use of a nonparametric analysis-of-covariance model on ranked data with effects for study group and region adjusted for baseline counts of gadolinium-enhancing T1 lesions. To protect the overall family-wise type I error rate of 5%, dose groups that differed significantly from placebo for the primary efficacy measures were compared with placebo for the three secondary MRI measurements with the use of a hierarchical testing procedure that was based on the Hochberg procedure. The sequential testing of the measurements was carried out only if the test for the previous measurement was significant.

Sensitivity analyses were conducted to assess the effect of baseline differences in disease characteristics on efficacy outcome measures. The results of these analyses are not reported here, since no material effects were shown. No interim analyses were conducted for this study.

RESULTS

PATIENTS

The demographic and clinical characteristics of the intention-to-treat population of 1326 patients was generally well balanced across the three study groups, although patients receiving 3.5 mg of cladribine per kilogram had a shorter mean duration of disease ($P=0.005$ for the overall comparison) (Table 1). Almost one third of patients had previously received disease-modifying therapy. Overall, 1184 patients (89.3%) completed the 96-week study (91.9% in the cladribine 3.5-mg group, 89.0% in the cladribine 5.25-mg group, and 87.0% in the placebo group) (Fig. 2 in the Supplemen-

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Variable	Placebo (N=437)	Cladribine	
		3.5 mg/kg (N=433)	5.25 mg/kg (N=456)
Age — yr			
Mean	38.7±9.9	37.9±10.3	39.1±9.9
Range	18–64	18–65	18–65
Female sex — no. (%)	288 (65.9)	298 (68.8)	312 (68.4)
Mean weight — kg	70.3±15.4	68.1±14.6	69.3±14.8
Race — no. (%)†			
White	429 (98.2)	425 (98.2)	446 (97.8)
Black	1 (0.2)	2 (0.5)	4 (0.9)
Other	7 (1.6)	6 (1.4)	6 (1.3)
Previous therapy with any disease-modifying drug — no. (%)‡	142 (32.5)	113 (26.1)	147 (32.2)
Disease duration from first onset — yr			
Mean	8.9±7.4	7.9±7.2§	9.3±7.6
Range	0.4–39.5	0.3–42.3	0.4–35.2
EDSS score¶			
0 — no. (%)	13 (3.0)	12 (2.8)	11 (2.4)
1 — no. (%)	70 (16.0)	75 (17.3)	80 (17.5)
2 — no. (%)	127 (29.1)	133 (30.7)	119 (26.1)
3 — no. (%)	96 (22.0)	108 (24.9)	108 (23.7)
4 — no. (%)	83 (19.0)	71 (16.4)	84 (18.4)
≥5 — no. (%)	48 (11.0)	34 (7.9)	54 (11.8)
Mean score	2.9±1.3	2.8±1.2	3.0±1.4
Gadolinium-enhancing T_1-weighted lesions			
Patients with lesions — no. (%)	128 (29.3)	138 (31.9)	147 (32.2)
Mean no. of lesions‖	0.8±2.1	1.0±2.7	1.0±2.3
Mean volume of T_2-weighted lesions — mm^3	14,287.6±13,104.8	14,828.0±16,266.8	17,202.1±17,467.7

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race was determined by the investigators.
‡ The most commonly used drugs were intramuscular interferon beta-1a (Avonex, 11.2% of patients), subcutaneous interferon beta-1b (Betaseron, 10.6% of patients), subcutaneous interferon beta-1a (Rebif, 9.4% of patients), and subcutaneous glatiramer acetate (Copaxone, 6.5% of patients).
§ P=0.005 for the overall comparison among the three groups.
¶ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10, with higher scores indicating a greater degree of disability.
‖ All imaging findings were based on all images that could be evaluated.

tary Appendix). A total of 1165 patients (87.9%) completed treatment (91.2%, 86.2%, and 86.3%, respectively). The mean time of participation in the study was 89.4 weeks (91.0, 89.4, and 87.8 weeks, respectively).

PRIMARY AND SECONDARY END POINTS

The annualized relapse rate at 96 weeks was significantly reduced in both cladribine groups, as compared with the placebo group (0.14 in the cladribine 3.5-mg group and 0.15 in the cladribine 5.25-mg group, vs. 0.33 in the placebo group), for relative reductions of 57.6% and 54.5%, respectively (P<0.001 for both comparisons) (Table 2 and Fig. 1A and 1C). The proportion of patients who remained relapse-free at 96 weeks was significantly higher in both cladribine groups (79.7% and 78.9%, respectively), as compared with the placebo group

(60.9%) (P<0.001 for both comparisons) (Table 2). In addition, the time to the first relapse was longer in both cladribine groups (hazard ratio in the 3.5-mg group, 0.44; 95% confidence interval [CI], 0.34 to 0.58; P<0.001; and hazard ratio in the 5.25-mg group, 0.46; 95% CI, 0.36 to 0.60; P<0.001 for both comparisons) (Table 2 and Fig. 1B). These improvements were achieved with a reduction in the odds of receiving rescue therapy with interferon beta-1a in the cladribine 3.5-mg group (60%) and the cladribine 5.25-mg group (69%), as compared with placebo (P=0.01 and P=0.003, respectively) (Table 2).

During the 96-week study, there was a relative reduction in the risk of 3-month sustained progression of disability in both cladribine groups,

Table 2. Clinical and Imaging End Points and Relapses during the 96-week Study (Intention-to-Treat Population).*

End Point	Placebo (N=437)	Cladribine	
		3.5 mg/kg (N=433)	5.25 mg/kg (N=456)
Relapse rate (primary end point)			
Annualized relapse rate (95% CI)	0.33 (0.29–0.38)	0.14 (0.12–0.17)	0.15 (0.12–0.17)
Relative reduction in annualized relapse rate for cladribine vs. placebo — %†		57.6	54.5
P value‡		<0.001	<0.001
Relapse-free rate			
Patients without relapse — no. (%)	266 (60.9)	345 (79.7)	360 (78.9)
Odds ratio for cladribine vs. placebo (95% CI)§		2.53 (1.87–3.43)	2.43 (1.81–3.27)
P value¶		<0.001	<0.001
Relapse at 96 weeks			
No. of relapses — no. of patients (%)			
0	266 (60.9)	345 (79.7)	360 (78.9)
1	109 (24.9)	69 (15.9)	77 (16.9)
2	44 (10.1)	13 (3.0)	13 (2.9)
3	15 (3.4)	5 (1.2)	5 (1.1)
≥4	3 (0.7)	1 (0.2)	1 (0.2)
P value‖		<0.001	<0.001
Need for rescue therapy			
Patients receiving rescue therapy — no. (%)	27 (6.2)	11 (2.5)	9 (2.0)
Odds ratio for cladribine vs. placebo (95% CI)§		0.40 (0.19–0.81)	0.31 (0.14–0.66)
P value¶		0.01	0.003
Time to first relapse			
15th Percentile of time to event — mo**	4.6	13.4	13.3
Hazard ratio for cladribine vs. placebo (95% CI)††		0.44 (0.34–0.58)	0.46 (0.36–0.60)
P value††		<0.001	<0.001
Time to 3-mo sustained change in EDSS score			
10th Percentile of time to event — mo**	10.8	13.6	13.6
Hazard ratio for cladribine vs. placebo (95% CI)††		0.67 (0.48–0.93)	0.69 (0.49–0.96)
P value††		0.02	0.03
Patients without a 3-mo sustained change in EDSS score			
Patients with no change — no. (%)	347 (79.4)	371 (85.7)	387 (84.9)
Odds ratio for cladribine vs. placebo (95% CI)§		1.55 (1.09–2.22)	1.46 (1.03–2.07)
P value¶		0.02	0.03

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Table 2. (Continued.)

End Point	Placebo (N=437)	Cladribine	
		3.5 mg/kg (N=433)	5.25 mg/kg (N=456)
Lesion activity on brain MRI			
Gadolinium-enhancing T_1-weighted lesions			
Mean no.	0.91	0.12	0.11
Relative reduction — %		85.7	87.9
Active T_2-weighted lesions			
Mean no.	1.43	0.38	0.33
Relative reduction — %		73.4	76.9
Combined unique lesions			
Mean no.	1.72	0.43	0.38
Relative reduction — %		74.4	77.9
P value‡‡		<0.001	<0.001

* EDSS denotes Expanded Disability Status Scale, and MRI magnetic resonance imaging.
† The relative reduction in the annualized relapse rate was calculated as the ratio of the difference in the annualized relapse rate between the placebo group and the cladribine group to the annualized relapse rate in the placebo group.
‡ The P value was based on a Wald chi-square test from an analysis of the number of relapses with the use of a Poisson regression model with fixed effects for treatment and region and the log of time in the study as an offset variable.
§ Odds ratios and associated 95% confidence intervals were estimated with the use of a logistic-regression model with fixed effects for study group and region.
¶ The P value was based on a Wald chi-square test from an end-point analysis with the use of a logistic-regression model with fixed effects for study group and region.
‖ The P value was based on a Cochran–Mantel–Haenszel test with adjustment for the baseline number of relapses.
** The 10th and 15th percentile values were estimated from the Kaplan–Meier survival curve.
†† The hazard ratio, 95% confidence intervals, and P values were based on a Cox proportional-hazards model with fixed effects for study group and region.
‡‡ The P value is for all comparisons with placebo for imaging measurements and was based on a nonparametric analysis-of-covariance model on ranked data with fixed effects for study group and region and the number of gadolinium-enhancing T_1-weighted lesions at baseline as a covariate.

as compared with placebo, with a 33% reduction in the cladribine 3.5-mg group (hazard ratio, 0.67; 95% CI, 0.48 to 0.93; P=0.02) and a 31% reduction in the cladribine 5.25-mg group (hazard ratio, 0.69; 95% CI, 0.49 to 0.96; P=0.03) (Table 2 and Fig. 1D). There were corresponding increases in the odds for remaining free of 3-month sustained disability progression in both cladribine groups, as compared with placebo (P=0.02 for the 3.5-mg group and P=0.03 for the 5.25-mg group) (Table 2).

Cladribine treatment resulted in significant reductions in measures of MRI activity, as compared with placebo. Patients in the cladribine 3.5-mg group and cladribine 5.25-mg group had fewer lesions per patient per scan than those in the placebo group for gadolinium-enhancing T1 lesions (mean number, 0.12 and 0.11, respectively, vs. 0.91), active T2 lesions (mean number, 0.38 and 0.33, respectively, vs. 1.43), and combined unique lesions (mean number, 0.43 and 0.38, respectively, vs. 1.72) (P<0.001 for all comparisons vs. placebo) (Table 2).

ADVERSE EVENTS

Lymphocytopenia (mostly graded as mild or moderate) was reported more frequently among patients receiving cladribine than among those receiving placebo (Table 3). Severe neutropenia (as rated by the investigators) was reported in three patients receiving cladribine (one in the 3.5-mg group and two in the 5.25-mg group), with severe thrombocytopenia and pancytopenia in one of the patients in the latter group, who also had an exacerbation of latent tuberculosis (see the Supplementary Appendix). There were no cases of severe anemia. The effects of cladribine on lymphocyte counts in the first and second 48-week periods are presented in Table 4. Figure 3 in the Supplementary Appendix shows the effects of

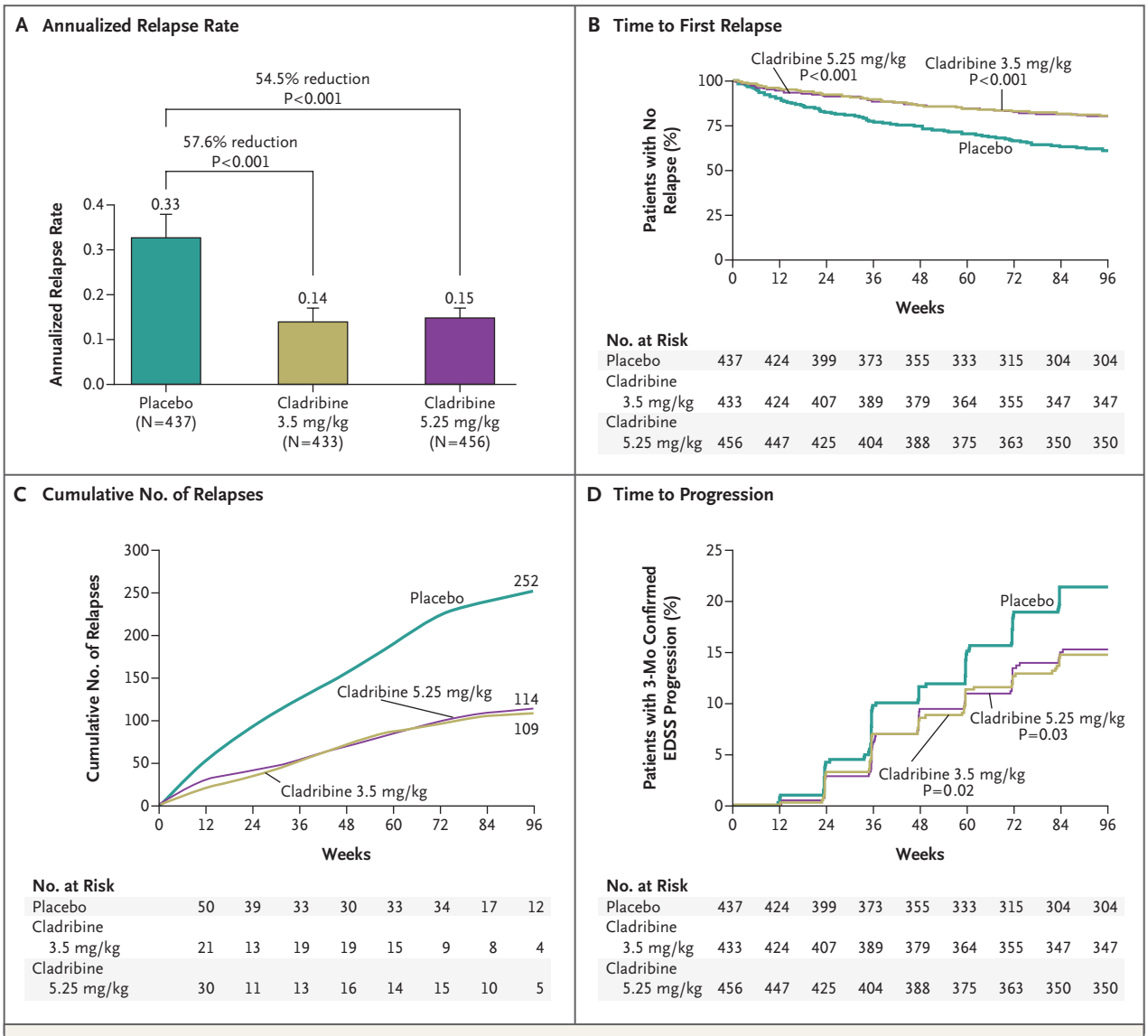

Figure 1. Efficacy Outcome Measures Relating to Relapse and Progression of Disability during the 96-Week Study Period (Intention-to-Treat Population).

Shown are the annualized rates of relapse (Panel A), Kaplan–Meier curves of the time to the first relapse (Panel B), the cumulative number of relapses over time (Panel C), and Kaplan–Meier curves of the time to 3-month sustained progression of disability, according to scores on the Expanded Disability Status Scale (EDSS) (Panel D). In Panel A, the T bars represent 95% confidence intervals. P values that are shown in Panels B and D are for hazard ratios and 95% confidence intervals during the 96-week period, as estimated with the use of a Cox proportional-hazards model with fixed effects for study group and region.

therapy on lymphocyte and neutrophil counts over the duration of the study. Maximal effects on lymphocyte, neutrophil, and platelet counts and hemoglobin levels are presented, according to laboratory criteria of the National Cancer Institute's Common Terminology Criteria for Adverse Events, in Table 1 in the Supplementary Appendix.

Infections or infestations were reported in 47.7% of the patients in the cladribine 3.5-mg group, 48.9% of those in the cladribine 5.25-mg group, and 42.5% of those in the placebo group, with most of the events graded as mild or moderate by investigators (99.6% and 98.6%, respectively, vs. 99.0%). Herpes zoster infections developed in 20 patients who received cladribine (including 1 with herpes zoster oticus): 8 patients in the

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Table 3. Adverse Events and Investigator-Assessed Severity at 96 Weeks (Safety Population).

Adverse Event	Placebo (N=435)	Cladribine		
		3.5 mg/kg (N=430)	5.25 mg/kg (N=454)	Combined Doses (N=884)
Any adverse event — no. of patients (%)	319 (73.3)	347 (80.7)	381 (83.9)	728 (82.4)
Most common adverse events — no. of patients (%)*				
Headache	75 (17.2)	104 (24.2)	94 (20.7)	198 (22.4)
Lymphocytopenia	8 (1.8)	93 (21.6)	143 (31.5)	236 (26.7)
Nasopharyngitis	56 (12.9)	62 (14.4)	58 (12.8)	120 (13.6)
Upper respiratory tract infection	42 (9.7)	54 (12.6)	52 (11.5)	106 (12.0)
Nausea	39 (9.0)	43 (10.0)	50 (11.0)	93 (10.5)
Ratio of mild-to-moderate events to severe events*				
Headache	186:3	258:6	260:5	518:11
Lymphoctyopenia	11:0	118:5	180:15	298:20
Nasopharyngitis	95:0	107:0	91:0	198:0
Upper respiratory tract infection	80:0	118:0	99:1	217:1
Nausea	48:1	73:1	68:1	141:2
Any serious adverse event — no. of patients (%)	28 (6.4)	36 (8.4)	41 (9.0)	77 (8.7)
Infections and infestations†	7 (1.6)	10 (2.3)	13 (2.9)	23 (2.6)
Neoplasms (benign, malignant, and unspecified)‡	0	6 (1.4)	4 (0.9)	10 (1.1)
Death§	2 (0.5)	2 (0.5)	2 (0.4)	4 (0.5)

* Listed are preferred terms from the *Medical Dictionary for Regulatory Activities* (MedDRA) for symptoms that were reported by at least 10% of the patients in any group. Investigators rated the severity of the event according to the following definitions: mild (the event or symptom is easily tolerated); moderate (the event or symptom interferes with or reduces the usual level of activity); and severe (the event or symptom causes substantial impairment of functioning, reduces the usual level of activity, or endangers the patient's life).

† This category, which is listed as a system organ class in MedDRA, includes three patients with herpes zoster among those receiving cladribine: one in the 3.5-mg group and two in the 5.25-mg group.

‡ This MedDRA system organ class includes five patients with benign uterine leiomyoma and one each of stage 0 cervical in situ carcinoma (considered precancerous), melanoma, ovarian carcinoma, pancreatic carcinoma, and myelodysplastic syndrome; the last was probably reactive bone marrow changes caused by tuberculosis infection and not true myelodysplasia (for details, see the Supplementary Appendix).

§ Four deaths occurred during the study and two after patients withdrew from the study. Causes of death were suicide and hemorrhagic stroke (in the placebo group), acute myocardial infarction and metastatic pancreatic carcinoma (in the cladribine 3.5-mg group), and drowning and cardiopulmonary arrest considered secondary to exacerbation of latent tuberculosis (in the cladribine 5.25-mg group).

3.5-mg group and 12 in the 5.25-mg group. All cases of herpes zoster were restricted and dermatomal in nature. There were three cases of primary varicella (one in each study group), all of which resolved without complication. Correlation analysis suggested that the lowest absolute lymphocyte counts in patients receiving cladribine were inversely correlated with the occurrence of infection (Spearman's correlation coefficient for both cladribine groups combined, −0.10; P=0.003).

Adverse events led to treatment discontinuation for 3.5% of patients in the cladribine 3.5-mg group, 7.9% of those in the cladribine 5.25-mg group, and 2.1% of those in the placebo group. The occurrence of lymphocytopenia and leukocytopenia led to treatment discontinuation in 0.9%, 4.2%, and no patients, respectively. The three study groups had similar rates of other events leading to the discontinuation of a study drug.

The incidence of serious adverse events was 8.4% in the cladribine 3.5-mg group, 9.0% in the cladribine 5.25-mg group, and 6.4% in the placebo group (Table 3, and Table 2 in the Supplementary Appendix). Infections or infestations were reported as serious adverse events in 2.3%, 2.9%, and 1.6% of patients, respectively. Herpes zoster was reported as a serious adverse event for three patients receiving cladribine (two in the 5.25-mg group). The occurrence of neoplasms (including those that were found to be benign, malignant, or unspeci-

Table 4. Effects of Cladribine on Lymphocyte Counts, According to Time Point (Safety Population).

Time Point	First Treatment Period		Second Treatment Period	
	3.5 mg/kg (N=430)	5.25 mg/kg (N=454)	3.5 mg/kg (N=430)	5.25 mg/kg (N=454)
Baseline				
Cell count/mm³				
Median	1900	1900		
Range (5th to 95th percentiles)	1100–3000	1050–3010		
Nadir (study week)	9	16	60	55
Cell count/mm³				
Median	1000	650	800	600
Range (5th to 95th percentiles)	490–2050	290–1250	370–1480	270–1400
Median reduction from baseline — %	45.8	64.0	55.9	64.6
End of treatment period (study week)	48	48	96	96
Cell count/mm³				
Median	1210	950	1060	910
Range (5th to 95th percentiles)	670–2080	500–1690	540–1960	480–1700
Median reduction from baseline — %	35.6	49.6	43.5	48.3

fied) was reported as a serious adverse event in 1.4% of patients in the cladribine 3.5-mg group and in 0.9% of those in the cladribine 5.25-mg group, as compared with no patients in the placebo group. These included five benign uterine leiomyomas that required inpatient hospital visits for treatment. There were three cases of cancer in the cladribine 3.5-mg group: a melanoma and carcinomas of the pancreas and ovary. A case of stage 0 cervical carcinoma in situ (considered a precancerous condition) was also reported in the cladribine 5.25-mg group. The time from the last course of therapy to diagnosis in these four patients was 2 months, 6 months, <9 months, and 7 months, respectively. For the patient with cervical carcinoma in situ, the relevant medical history included a positive test for human papillomavirus type 16 at 3 years before diagnosis. A choriocarcinoma was diagnosed in one patient in the cladribine 5.25-mg group approximately 9 months after completion of the study.

There were four deaths during the study and two after study discontinuation, equally distributed across the three study groups. Causes of death were acute myocardial infarction and metastatic pancreatic carcinoma in the cladribine 3.5-mg group, drowning and cardiopulmonary arrest that was considered secondary to exacerbation of latent tuberculosis in the cladribine 5.25-mg group, and suicide and hemorrhagic stroke in the placebo group (for details, see the Supplementary Appendix).

DISCUSSION

Our study showed that short-course therapy with cladribine tablets provided rapid and sustained treatment benefits for patients with relapsing–remitting multiple sclerosis during a 96-week period. As compared with placebo, treatment with cladribine resulted in reductions in the rates of clinical relapse and in the risk of disability progression and in the suppression of active inflammatory lesions, as visualized on MRI. Both the regimens of 3.5 mg and 5.25 mg per kilogram appeared to be equally efficacious.

The most commonly reported adverse event was lymphocytopenia. There was an inverse correlation between the incidence of infection and a patient's lowest absolute lymphocyte count in the combined cladribine groups. Activation of latent herpes zoster occurred in 20 cladribine-treated patients. One patient who was treated with cladribine had reactivation of latent tuberculosis and died. The use of cladribine may have contributed to this reactivation, and tuberculosis screening measures

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were subsequently implemented in ongoing clinical trials to rule out latent or active infection before treatment or retreatment. Cancers were isolated cases across different organ systems, and given the small number, it is not possible to establish a risk for the use of cladribine.

In conclusion, our study showed that short-course treatment with cladribine tablets for only 8 to 20 days per year provided a significant benefit for patients with relapsing–remitting multiple sclerosis with respect to the rate of relapse, disability progression, and MRI measures of disease activity during the 96-week study period. The benefits of treatment will need to be weighed against the risks.

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