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-generated 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

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.

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 meth-

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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