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sured by Scripps Neurological Rating Scale (SNRS; 7) (in 10-point intervals). The stratified groups were then randomized in blocks of four to either the placebo arm or the cladribine arm. In all, 27 patients were randomized onto the cladribine arm and 25 onto the placebo arm. Throughout the study, patients, neurologists, nurses, and the neuroradiologist remained blinded to treatment assignment. A pharmacist was informed of patient assignment by code in order to dispense placebo or the appropriate dose of cladribine to each patient.

In all patients, clinical neurological exams plus SNRS and EDSS rating scales were performed at baseline and repeated by the same neurologist every month for the first year, every 3 months for the second year, and within 48 hr or less of report by a patient of a relapse. A clinical relapse was defined as the appearance of new symptoms or worsening of an existing symptom, attributable to MS and accompanied by objective worsening of neurological findings. To be scored as a relapse the alterations must have been preceded by disease stability or improvement lasting for at least 30 days, and the worsening must have lasted at least 24 hr and occur in the absence of fever. Relapse severity was rated as follows: 1) mild relapse—decrease in SNRS of 1–7; 2) moderate relapse —decrease in SNRS of 8–14; or 3) severe relapse—decrease in SNRS of 15 or greater.

Magnetic resonance imaging (MRI) of the brain was performed on a 1.5 T Signa scanner (General Electric, Milwaukee, WI) for each patient at baseline, and then monthly for the first year and every 6 months the second year. T1-weighted scans were obtained in the sagittal and axial planes. Axial scans of 3 mm thickness and zero interslice gaps were done about 10 min after the intravenous injection of gadopentetate dimeglumine (Magnevist, Berlex Laboratories). Special attention was given to careful repositioning of patients to guarantee reproducible slice positions. The regions of contrast enhancement on T1-weighted scans were outlined by hand on filmed images. All scans were interpreted and marked by the same neuroradiologist (J.Z.), who had no knowledge of patient treatment assignment. These were then duplicated by a technologist using the taped raw data and a computer workstation [ANALYZE (8), Rochester, MN]. Quantitation of MRI findings involved the determination of lesion areas on the consecutive sections of the T1-weighted scans as interpreted by one of two skilled technologists, then calculation of volumes by assuming homogeneity of lesions across the sections. Initially, the taped raw data from the individual scans were read into a volume-rendering software program, ANALYZE, running on a Hewlett-Packard 712/60 workstation. Our methodology for lesion area determination is a semiautomated quantitative techni
adapted from Wicks et al. (9) and Filippi et al. (10)

Drug Administration

In contrast to our earlier study of intravenous cladr
ine in progressive MS (5), the drug was administe
subcutaneously because of greater ease of administ
tion and because it has now been established that
pharmacological properties and response rates
cladribine in lymphoproliferative diseases are
same if the drug is given either intravenously or su
cutaneously (11). Each patient received a course
five consecutive daily subcutaneous injections
cladribine, 0.07 mg/kg/day or an equivalent volu
of saline placebo, fractionated into two or three inje
tion sites, and given monthly for 6 months for a to
cumulative dose of 2.1 mg/kg of cladribine. A co
plete blood count was obtained before each month
course of treatment and reviewed by the pharmaci
and the next dose of cladribine was given only
blood count safety criteria were met according to
algorithm designed for this purpose by one of
(E.B.; Table 1). If these criteria were not met, a pl
cebo dose was substituted. The study design includ
eight monthly courses. The last two courses ordinari
consisted of placebo, but if a drug dose had be
omitted because of blood count inadequacy, then a
tive drug could be given at month 7 or 8 instead
placebo.

Statistical Considerations

Two primary outcome measures were identified:
the joint frequency and severity of clinical relapses
judged by neurological examination; and 2) the nun
bers of enhancing lesions on T1-weighted MRI brai

Table 1. Pretreatment safety criteria for monthly courses of cladribine in multiple sclerosis

1. Platelet count must be:
   a. 200,000 or higher, or
   b. Between 150,000 and 200,000 and represent more than 50% of previous pretreatment platelet count, or
   c. Between 125,000 and 150,000 and represent at least 80% of previous pretreatment platelet count
2. Absolute granulocyte count must be greater than 1000
3. Hemoglobin level must not have declined:
   a. More than 1.5 g/dl from previous monthly pretreatment level, or
   b. 3 g/dl or more from baseline

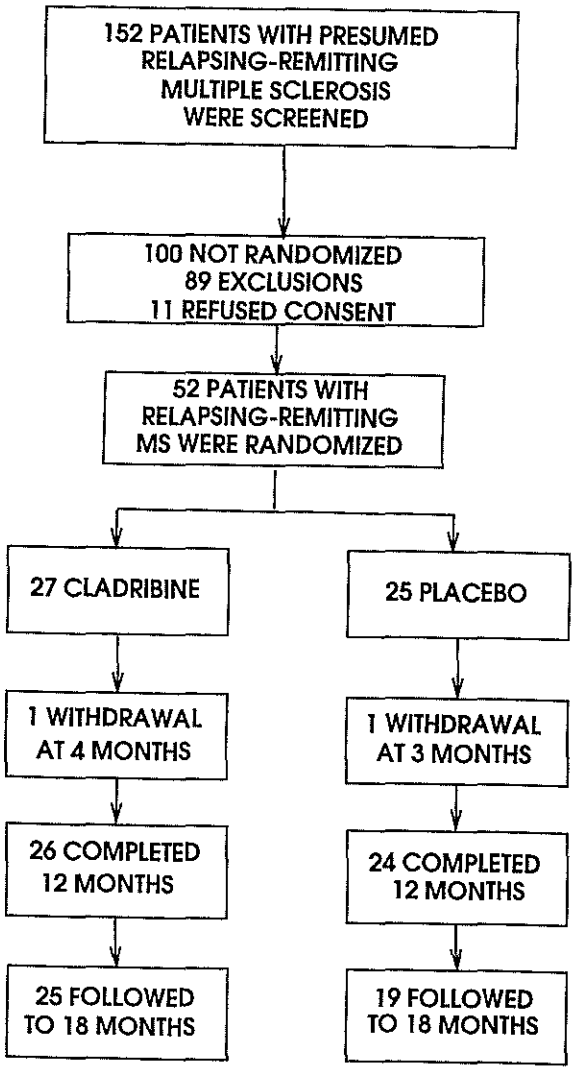

Figure 1. Trial profile of the cladribine relapsing-remitting MS clinical trial.

Because of potential bias, information from these patients concerning their frequency and severity of exacerbations subsequent to the point of unblinding is not used in the calculation and comparison of exacerbation rates between the two treatment groups.

Demographic and Baseline Characteristics in the Two Treatment Groups after Randomization

The two groups were similar in terms of baseline clinical characteristics (Table 2). Each group had an approximate 2:1 female-to-male preponderance and comparable mean age, disease duration, and baseline EDSS. Patients randomized to cladribine therapy averaged a slightly greater number of exacerbations in the 12 months prior to study entry than patients randomized to placebo

Table 2. Baseline demographic and clinical characteristics

	Placebo (n = 25)	Cladrib (n = 2
Sex		
Male	7	9
Female	18	18
Race		
White	25	24
Other	0	3
Age (years)		
Mean	39.8	43.4
25th percentile	36.5	38.5
50th pecentile	41	44.5
75th percentile	44	49.5
Range	31–52	30–52
Years with symptoms		
Mean	9.1	10.2
25th percentile	3.5	4.5
50th pecentile	9	8
75th percentile	12.5	12.5
Range	1–25	1–29
Number of exacerbations in previous year		
1	13	5
2	5	16
3 or 4	7	6
Baseline EDSS		
Mean	3.8	3.9
25th percentile	2.5	2.3
50th pecentile	3.5	5.5
75th percentile	5.3	5.5
Range	2–6.5	2–6.5
Baseline SNRS		
Mean	75.8	76.1
25th percentile	67	66
50th pecentile	75.5	78.5
75th percentile	86	86.5
Range	54–98	41–93

EDSS, Extended Disability Status Score. SNRS, Scripps Neurological Rating Scale.

Effect of Cladribine on Outcome Measures

Figure 2 depicts the frequency and severity of exacer bations for all patients enrolled in the study. W examined the joint distribution of frequency and se verity over months 7 through 12 for treatment com parisons: on the basis of our prior experience (17), w expected the maximum immunosuppression on clad ribine therapy would not be achieved prior to montl 7. Using the extended Mantel-Haenszel procedure, w found that there is a statistically significant reductio in the frequency and severity of exacerbations in th cladribine group compared to the placebo group ove months 7 through 12 ($Q_M = 2.30$, $2p = .021$). Ove

the 1-year period from month 7 through month 18. Over this extended period, the exacerbation rate in the cladribine group was 0.66 per year (95% CI, 0.37–1.05) compared to 1.34 per year in the placebo group (95% CI, 0.90–1.93).

Figure 3 compares the frequency and severity of relapses at 6-month intervals during the study with the frequency of relapses in the 12 months preceding treatment with drug or placebo. It is apparent that there was striking improvement in the first 6 months of the study, when injections of placebo or cladribine were being given 5 days of each month, regardless of whether the patients received placebo or active drug. When injections were stopped, the frequency of relapses in the placebo group returned to its baseline, pretreatment frequency, but the frequency and severity of relapses continued to decline in the patients who received cladribine.

MRI results (Fig. 4, Table 3) revealed complete suppression of enhancing lesions after study month 6 in the cladribine group, whereas lesion enhancement persisted in the placebo group. Formally, with regard to the primary outcome measure at 12 months, there is a highly significant decrease in the occurrence of enhancing lesions at 12 months relative to baseline in the cladribine group ($2p < .0003$ by McNemar's test). In contrast, there is a slight increase in the occurrence of enhancing lesions at 12 months relative to base in the placebo group ($2p = .109$ by McNemar's t and, the frequency of enhancing lesions is sig cantly greater at 12 months in the placebo group in the cladribine group ($2p = .0001$ by Fisher e test). In secondary analyses, we find a significan duction in the frequency of enhancing lesions ex enced by the cladribine group relative to baselin ready at month 7 and persisting at month 18 (2 .0005 by McNemar's test at each time point). M over, the frequency of enhancing lesions in the cebo group is already significantly greater than th the cladribine group by 7 months ($2p = .000$ Fisher) and remains so at 18 months ($2p = .00$ Fisher). No significant predictors of enhancing le presence other than treatment were found by log regression.

We found no significant differences between treatment groups in either EDSS or SNRS scores secondary outcome parameters, over 18 months (p for each; Fig. 5).

Adverse Events and Side Effects

Infections were limited to an episode of mild segm tal herpes zoster that occurred in two cladrib

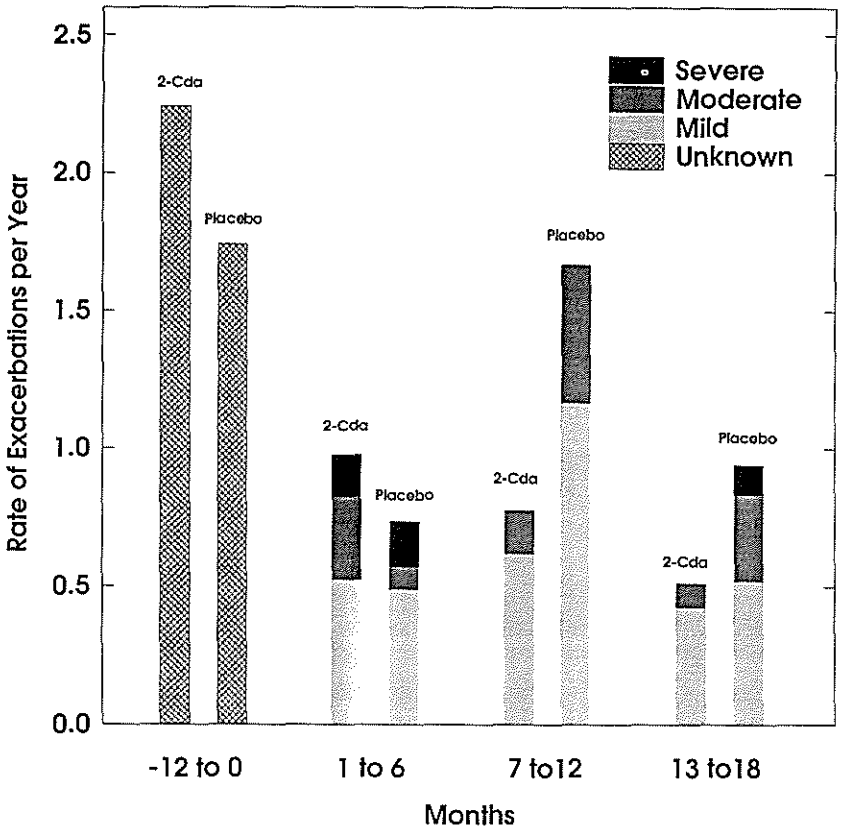

Figure 3. Rates of exacerbations for two treatment groups.
The number of exacerbations for the prior to initiation of treatment was obta from the patient's history. Over the cour the trial itself, exacerbations were d mented by the neurologist and classifie mild, moderate, or severe as explained i text. For purposes of comparison, rates presented as relapses per year.

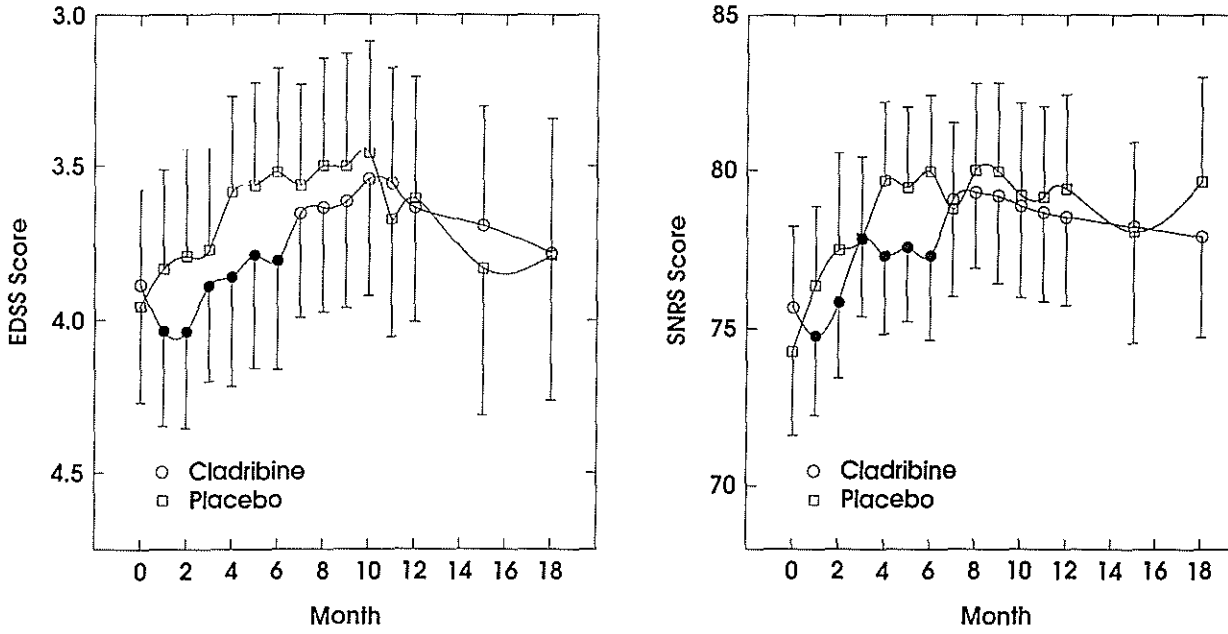

Figure 5. Changes in the Kurtzke (EDSS) and Scripps (SNRS) rating scores.
Solid symbols indicate when cladribine was administered. Means and pointwise standard error bars are shown.

gressive MS multicenter study and no significant toxicity was observed.

The results in relapsing-remitting MS, as reported in the current study, indicate that cladribine given subcutaneously at a total dosage of 2.1 mg/kg appears to be safe and effective in reducing the rate and severity of clinical exacerbations for at least the relatively short duration of the study. Particularly striking was the placebo effect noted in the first 6 months of our study, when patients were receiving injections; the relapse frequency dropped to about one half in both groups of patients. In the second 6 months, however, when no injections were given but after immunosuppression had been achieved in the drug-treated group, the relapse frequency returned to baseline in patients who had received placebo, but patients who had received drug continued to enjoy relative freedom from exacerbations, an effect that continued into the second year of the study.

Our primary analyses are predicated on outcomes at 1 year following randomization. During this period, all patients received the treatment to which they had been randomized; that is, treatment allocation and treatment actually received were identical for everyone. Two patients, one randomized to placebo and the other to cladribine, withdrew from the study during the first year. Hence, the attrition rate was <5% on each arm over the formal length of the trial. The results of our primary analyses at 1 year, comparing the joint frequency and severity of exacerbations between the treatment groups, and comparing the frequenci of enhancing lesions, are insensitive to the loss of i formation from these patients. With regard to the se ond primary end point, the presence of enhancing l sions of T1-weighted scans, it is clear from Table that even under the least favorable scenario f cladribine—no enhancing lesions in the placebo wit drawal, but enhancing lesions in the cladribine wit drawal—the favorable outcome of cladribine therap relative to placebo at 1 year would remain ove whelmingly significant. The lack of any demonstrab difference in neurological disability (EDSS a SNRS scores) between the cladribine and placeb groups is of uncertain significance since neither trea ment group, including the placebo group, showed si nificant worsening over the duration of the study.

The almost complete suppression of MR enhancing lesions with cladribine is a very robust trea ment effect similar to that previously reported wi cladribine in progressive MS (5,6,18) and exceedi the effect of interferon beta-1a (19). Since enhanc ment of MRI lesions is thought to reflect active di ease (20), the question arises as to how some cladribin treated patients continued to have clinical relapse but with no apparent lesion enhancement on seri MRI scans.

The mechanism of action of the beneficial effe of cladribine on MS is presumably related to the s lective and sustained depletion of lymphocytes. In previous study of cladribine in chronic progressiv

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