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Cladribine

Use in Therapy of Multiple Sclerosis

John S. Romine,[1] *Jack C. Sipe*,[1] *James A. Koziol*,[2] *Jack Zyroff*,[3] *Robert McMillan*[2] and *Ernest Beutler*[2]

1 Division of Neurology, Scripps Clinic and Research Foundation, La Jolla, California, USA
2 Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California, USA
3 Division of Radiology, Scripps Clinic and Research Foundation, La Jolla, California, USA

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Summary

Cladribine is a novel drug that selectively depletes lymphocytes and may be able to destroy the activated immunocytes that damage the central nervous system in multiple sclerosis. Our initial controlled studies have shown a beneficial, although temporary, dose-related effect of cladribine on the course of chronic progressive multiple sclerosis.

Peak improvement in median Scripps Neurological Rating Scale (SNRS) neurological performance scores, followed by gradual decline, occurred at month 14 after initiation of treatment with a 2.8 mg/kg total dose and at month 7 after initiation of treatment with a 1.4 mg/kg total dose. A marked decrease in the presence of enhanced magnetic resonance imaging lesions was observed at both dose levels.

Adverse effects are also dose-related. Mild segmental herpes zoster or transient marrow suppression occurred in some patients treated at the higher total dose, whereas no problems of this kind were observed at the lower total dose.

It is our hope that studies that are presently under way will establish cladribine as a practical therapeutic option for patients with all non-benign forms of multiple sclerosis.

The fundamental cause of multiple sclerosis is still unknown, but there is persuasive circumstantial evidence that immunopathological mechanisms play an important role in the inflammatory demyelination of the central nervous system (CNS) which is the hallmark of the disease.[1] Suppression and/or 'modulation' of the immune system is therefore a rational means of therapy for multiple sclerosis.[2]

Although interferon-β has recently been shown to decrease the frequency and severity of relapses in the relapsing-remitting form of multiple sclerosis,[3] no clearly satisfactory treatment by immunosuppression or any other method has yet been

Table I. Completed and ongoing clinical trials of cladribine in the treatment of multiple sclerosis

Trial	Type of multiple sclerosis	Blinded/ crossover	Dosage and duration (daily dose × number of days)	Route	Number of courses	Trial location	Comments and references
1[a]	CP	No/no	0.087 mg/kg × 7	IV	6	Scripps	Feasibility study in 4 patients in 1990
2[a]	CP	Yes/yes	0.1 mg/kg × 7	IV	4	Scripps	Part I of double-blind crossover study[12]
			0.1 mg/kg × 7 0.05 mg/kg × 7	IV IV	1 2	Scripps	Part II of double-blind crossover study[13]
3[b]	RR	Yes/no	0.07 mg/kg × 5	SC	6	Scripps	
4[b]	CP	Yes/no	0.07 mg/kg × 5	SC	2 and 6	Multicentre in US and Canada	
5[b]	CP	Yes/no	0.05 mg/kg × 5	SC	4	Scripps	Retreatment study of patients from trial 2[21]
6[b]	RR	Yes/no	5mg × 5 10mg × 5	SC Oral	6	Polish Academy of Science	

a Completed study.

b Ongoing study.

Abbreviations: CP = chronic progressive; IV = intravenous; RR = relapsing remitting; SC = subcutaneous.

found for patients with chronic progressive multiple sclerosis (CPMS). Previous trials of treatment in CPMS have involved broad-spectrum immunosuppressive drugs such as cyclophosphamide[4] and methotrexate.[5] The modest benefit observed with these drugs has been generally counterbalanced by concerns over toxicity.

One current hypothesis of multiple sclerosis pathogenesis is that activated T lymphocytes pass from the bloodstream into the multiple sclerosis plaques in the CNS. These activated cells, regardless of their immune specificity, may directly or indirectly damage myelin and/or oligodendrocytes. Therefore, the selective depletion of lymphocytes in multiple sclerosis might be beneficial if it could be accomplished safely. For these reasons, a new type of drug, cladribine (2-chlorodeoxyadenosine, Leustatin®), was selected for trial in CPMS because of its properties of relatively selective production of lymphopenia with a favourable toxicity profile as compared with other antilymphocyte drugs.[6]

Cladribine is an adenosine deaminase–resistant purine nucleoside that was developed by Carson et al.[7] at Scripps Clinic and Research Foundation. The drug was designed to simulate the immunodeficient condition seen in the rare disorder of hereditary adenosine deaminase deficiency by causing high levels of deoxynucleotides to accumulate in lymphocytes, thus resulting in cell death. In contrast with other antilymphocyte agents, cladribine has the ability to kill both resting and dividing cells.[8]

The use of cladribine in CPMS was considered following pioneering clinical studies with cladribine at the Scripps Clinic in the treatment of various lymphoid neoplasms and leukaemia.[9] The most dramatic positive results were seen in hairy cell leukaemia, in which 86% of patients experienced a durable and complete remission after a single treatment with cladribine.[6] Cladribine is also presently under evaluation at our institution in a variety of autoimmune disorders, including Coomb's positive haemolytic anaemia, immune thrombocytopenia, rheumatoid arthritis and inflammatory bowel disease.

The bioavailability of cladribine is the same by either continuous intravenous or intermittent subcutaneous administration, and is halved when given by the oral route.[10] A detailed discussion of the clinical pharmacokinetics of cladribine has been presented elsewhere.[11]

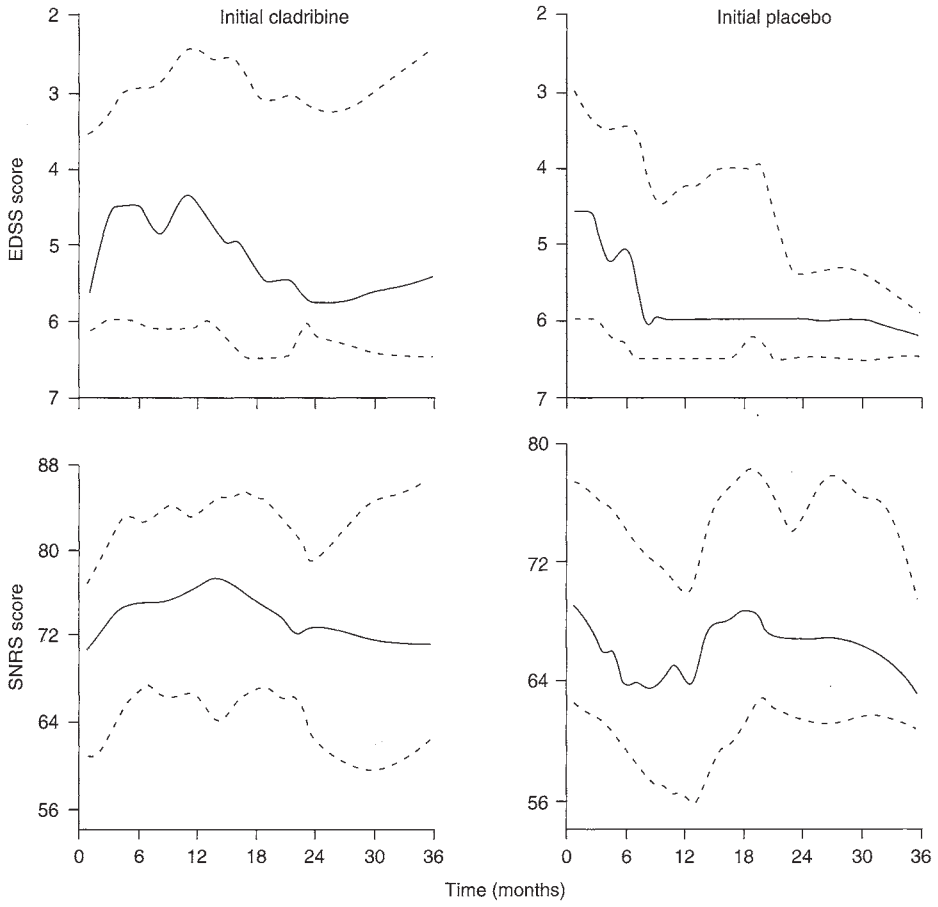

Fig. 1. Kurtzke Extended Disability Status Scale (EDSS) [**top**] and Scripps Neurological Rating Scale (SNRS) [**bottom**] scores of 48 patients with chronic progressive multiple sclerosis treated with cladribine in a double-blind crossover study. The initial cladribine group (**left**) received cladribine 0.7 mg/kg as a continuous intravenous infusion over 7 days in each of 4 successive months. The initial placebo group (**right**) was given cladribine 0.7 mg/kg as the first monthly infusion in month 13, and 2 subsequent 7-day infusions of 0.35 mg/kg in months 14 and 15. Medians (solid lines) and interquartile ranges (broken lines), smoothed with the nonparametric procedure LOWESS, are shown.

1. Results in Chronic Progressive Multiple Sclerosis

An initial feasibility study with 4 patients in 1990 was encouraging, and we subsequently conducted a double-blind crossover study of the effect of cladribine in CPMS (table I). To date, this is the only controlled study of cladribine in multiple sclerosis to be completed; the results have been published in 2 parts.[12,13]

In this study, 48 patients with CPMS were paired by age, gender and disease severity. Pair members were randomly assigned to receive either cladribine or placebo treatment via surgically implanted venous access devices. Patients on the cladribine arm were given monthly 7-day continuous intravenous infusions of cladribine 0.1 mg/kg/day (0.7 mg/kg/course) for a total of 4 courses (total dose 2.8 mg/kg). Patients on the placebo arm were given saline intravenously in an identical fashion. Double-blind masking was maintained; patients, neurologists, neuroradiologists and nurses had no knowledge of which medication

a patient was receiving. Patients were examined monthly and 2 neurological performance scores were recorded [Kurtzke Extended Disability Status Scale (EDSS)[14] and Scripps Neurological Rating Scale (SNRS)[15]].

Over 12 months, analysis of SNRS and EDSS scores showed progressive deterioration during the first year in patients receiving placebo, while the median SNRS and EDSS scores of patients receiving cladribine improved modestly. Absolute changes in neurological scores were favourable in both EDSS ($p = 0.013$ at 12 months) and SNRS ($p = 0.001$ at 12 months) scoring systems (fig. 1). Statistical significance in favour of cladribine was also established when 12 months of data were analysed by Kaplan-Meier time-to-failure plots (fig. 2).[13]

Blinding was maintained and the study was continued for a second year of treatment and observation. However, patients were crossed over to opposite treatment arms. Patients treated with cladribine in the first year received placebo in the second year, and vice versa. However, the dosage of cladribine was reduced to one-half of that given during the first year. The reduced total dose of cladribine 1.4 mg/kg was administered by continuous intravenous infusion in divided doses as follows: 0.7 mg/kg for the first monthly course, 0.35 mg/kg for the second and third courses, and saline placebo for the fourth course. Patients who had received cladribine in the first year were given 4 monthly infusions of saline placebo.

Results from the second year are also illustrated in figure 1. Comparison of data from years 1 and 2 of the study reveals that patients who had first received placebo and then crossed over to treatment with the lower dose of cladribine (1.4 mg/kg) show a trend of improvement in SNRS scores similar to that seen in patients treated with the full (2.8 mg/kg) dose. Similar comparison also suggests

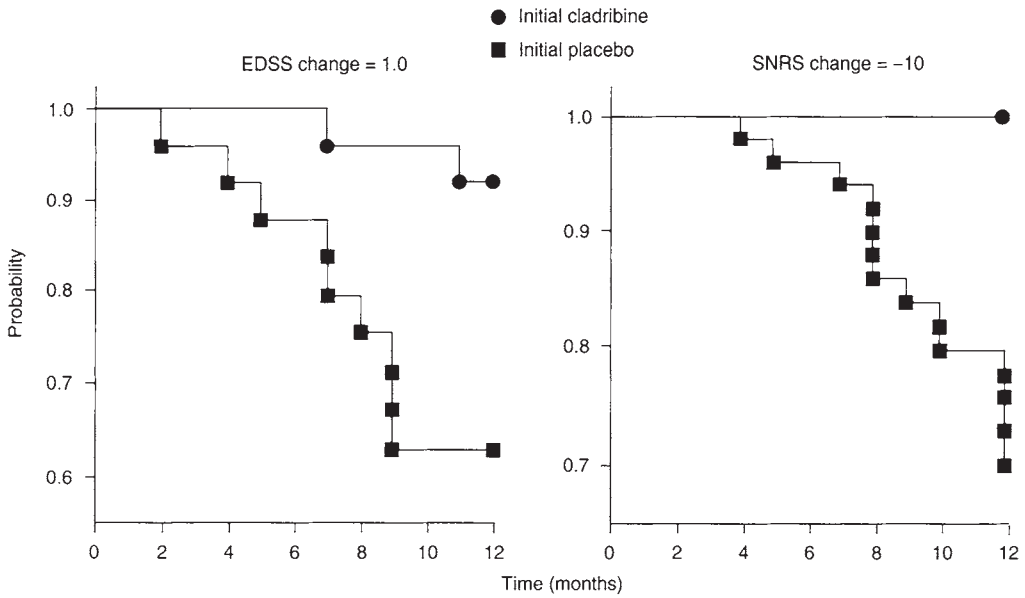

Fig. 2. Kaplan-Meier time-to-failure plots of patients with chronic progressive multiple sclerosis treated with cladribine in a double-blind crossover study. (**Left**) Time to failure as defined by an increase of Kurtzke Extended Disability Status Scale (EDSS) score by 1.0 point on at least 2 consecutive months, considering the first month of change as the time of event. (**Right**) Time to failure as defined by a decrease of Scripps Neurological Rating Scale (SNRS) score by 10 points on at least 2 consecutive months, considering the first month of change as the time of event. The difference in time to failure estimated by log-rank statistics was significant for both scoring systems in favour of cladribine (EDSS, $p = 0.0148$; SNRS, $p = 0.001$).

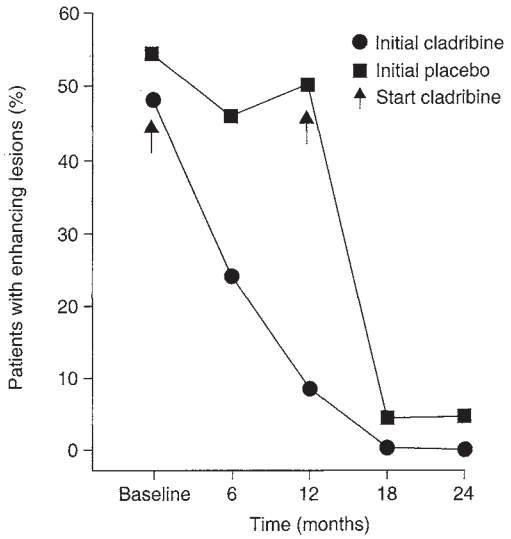

Fig. 3. Proportion of patients with enhancing lesions over the course of a double-blind crossover study of cladribine treatment of chronic progressive multiple sclerosis. The difference was significant in favour of cladribine at 12 and 24 months ($p < 0.001$ by McNemar's test).

that stabilisation of disease may be of shorter duration with the lower dose of cladribine. Peak improvement of median SNRS scores, followed by gradual decline, occurred at month 14 after initiation of treatment with the 2.8 mg/kg total dose and at month 7 after initiation of treatment with the 1.4 mg/kg total dose. Statistical analysis of the variance of paired differences in EDSS and SNRS scores from year 2 of the study again confirmed significant treatment effects in favour of cladribine.[16]

Magnetic resonance imaging brain scans were obtained after intravenous gadopentetate dimeglumine at baseline and at 6, 12, 18 and 24 months. Volumetric analysis of demyelinated (T_2-weighted) lesions revealed no significant differences between the cladribine and placebo groups. However, a highly significant difference in favour of cladribine was documented when the number of 'active' lesions (lesions enhanced by gadopentetate) were analysed (fig. 3). Approximately one-half of the patients in both the initial cladribine-treated and the initial placebo-treated groups had enhancing lesions at baseline. At 18 and 24 months after initiation of treatment with cladribine 2.8 mg/kg total dose, no patient had lesion enhancement. In patients treated initially with placebo, lesion enhancement persisted at the same percentage level at months 6 and 12, but after treatment with cladribine 1.4 mg/kg total dose, lesion enhancement was subsequently observed in only a single patient.

2. Adverse Effects

As of June 1995, a total of 125 multiple sclerosis patients (both chronic progressive and relapsing/remitting multiple sclerosis) have been treated at Scripps Clinic. The adverse events observed to that date in association with cladribine treatment are summarised in table II. Most patients had no obvious drug-related symptoms or signs in association with the administration of cladribine. However, 8 patients, all treated with the full 2.8 mg/kg dose, developed mild segmental herpes zoster. No other opportunistic infections occurred. 3 patients treated with the 2.8 mg/kg dose developed transient bone marrow suppression with low platelet counts; 2 of these patients required hospitalisation for red cell and platelet transfusion. One patient died of acute fulminant hepatitis B during the second month on cladribine, an event previously reported and considered to be probably unrelated to treatment.[12]

The details of the effect of cladribine on blood counts in these patients are reported elsewhere.[17] As expected, profound and prolonged lymphocyte depletion (most notably CD4+ cells) occurred in cladribine-treated patients; other blood cellular components were less affected. Granulocyte counts showed only a minor decline and the average haemoglobin level declined moderately, with significant anaemia due to transient bone marrow suppression in only a single patient. However, red cells generally became macrocytic, especially at the higher dose levels. Average platelet counts declined to a low of around 1.5×10^9/L, with recovery to near normal levels by 12 months after treatment. Monocyte counts dropped within days of drug ad-

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