

Cladribine

A Review of its Use in Multiple Sclerosis

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Summary

Cladribine is a deaminase-resistant deoxyadenosine analogue that selectively reduces lymphocyte counts. The drug is an effective therapy for selected haematological malignancies and is being tested in patients with multiple sclerosis (MS),

in whom the antilymphocytic effects of the drug may reduce the autoimmune destruction of myelin.

With activity against resting and dividing cells that express high deoxycytidine kinase activity, cladribine causes prolonged, profound suppression of lymphocyte counts. Subcutaneous cladribine is 100% bioavailable and has no local tissue toxicity. Dosages used in clinical trials in patients with MS are in the range of 0.05 to 0.07 mg/kg/day subcutaneously for 5 days each month for 2 to 6 months.

Temporary improvement or no change in neurological functioning and improvements in CNS lesions detected by gadolinium-enhanced magnetic resonance imaging (MRI) have been seen after cladribine use in patients with chronic progressive (CPMS) and relapsing-remitting (RRMS) forms of MS. In a randomised double-blind study of 24 pairs of patients, improvement or stabilisation of CPMS for ≈ 2 years was observed in cladribine-treated patients, whereas the disease progressed in placebo recipients. Another study of 159 patients found no progression in either the treated or placebo control group. In both studies, marked improvements were seen in gadolinium-enhanced CNS lesions. Cladribine-associated improvements in neurological functioning were also seen in some patients with RRMS in one study, which also noted a reduction in the frequency and severity of relapses. In this and a separate RRMS study, cladribine resulted in the regression of CNS lesions on MRI.

Bone marrow suppression is the main dose-related toxicity; in patients with MS, use of low total cladribine dosages appears to limit myelosuppression. Although thrombocytopenia is of concern with higher-dose regimens (i.e. 2.8 mg/kg total dose) in patients with MS, granulocyte counts and haemoglobin levels appear to be largely unaltered. Cladribine treatment is also associated with culture-negative fever and a risk of infections in patients with haematological malignancies.

Conclusions: Further study of cladribine is needed to confirm present results in wider numbers of patients treated or followed up for longer durations, define optimum treatment and retreatment schedules for the drug and compare it with other agents. Nonetheless, cladribine therapy appears to have the potential to slow the progression of MS, reduce CNS lesions in patients with either the chronic progressive or relapsing-remitting forms of the disease and improve neurological functioning in some of these patients.

1. Rationale for the Use of Cladribine in Multiple Sclerosis

Multiple sclerosis (MS) is characterised by clinical signs and symptoms of CNS demyelination including optic neuritis, diplopia, muscle weakness, spasticity and eventual loss of ambulatory function. The disease may have relapsing and remitting stages (RRMS) or can be chronic and progressive (CPMS).^[1,2] However, progressive disease may occur without a relapsing-remitting stage (primary progressive) or may follow a relapsing-remitting stage (secondary progressive).^[3] The disease is

highly variable in its course, and although it causes considerable disability, it does not greatly reduce life expectancy, except in patients with severe disability.^[4]

A diagnosis of MS must be based on symptoms characteristic of at least 2 CNS lesions. Tests that assist in diagnosis and evaluation of the progression of MS include examination of the CSF for the presence of oligoclonal bands of IgG and magnetic resonance imaging (MRI) for CNS lesions.^[5] Neurological impairment is often assessed using the Kurtzke extended disability status scale (EDSS), although the Scripps neurological rating scale

(SNRS) and other similar tests have also been used.^[2] For a more detailed description of the functions of these tests, see section 3 and the review by Waubant and Goodkin.^[2]

Cladribine (2-chloro-2'-deoxyadenosine) is an adenosine deaminase-resistant analogue of deoxyadenosine. After phosphorylation to cladribine triphosphate within cells by the enzyme deoxycytidine kinase (dCK), it is incorporated into DNA, where it takes the place of adenosine triphosphate and effectively halts cell replication.^[6] Phosphorylated cladribine can be dephosphorylated (and therefore inactivated) by 5'-nucleotidase (5-NT). Of various cells of the body, lymphocytes are most subject to the effects of cladribine because they have a higher ratio of dCK to 5-NT than other cells. This and other mechanisms confer on cladribine specific antilymphocytic effects that are of clinical utility in the treatment of haematological malignancies (reviewed by Bryson & Sorkin^[6]).

Although MS is thought to be a lymphocyte-dependent autoimmune disease, the specific antigens and triggering agents involved in the disease are unknown, so treatments are nonspecific.^[7] The rationale for the use of cladribine in MS is that autoantigen-specific T lymphocytes are thought to be activated peripherally before migrating to the CNS, where they mediate damage to myelin.^[8] This suggests that a cladribine-induced reduction in the number of lymphocytes may help to slow progression of the disease. The efficacy of cladribine in the treatment of MS has been studied and the evidence relating to its potential use in this disease is reviewed here.

2. Pharmacology

2.1 Pharmacodynamics

2.1.1 Pharmacodynamic Effects and Mechanism of Action

The major pharmacodynamic effects of cladribine are on blood cells and blood progenitor cells, which express high levels of dCK. dCK levels, which correlate with the degree of cladribine phosphorylation, are high in normal leucocytes (120 ng dCK/mg protein) and low in other tissues such as

stomach mucosa (6 ng/mg).^[9] Cladribine also markedly and dose-relatedly inhibits lymphocyte colony-forming and myeloid progenitor cells from normal human peripheral blood and bone marrow *in vitro*.^[10] Bone marrow suppression is a dose-limiting adverse effect of cladribine (see section 4).

Cladribine is active against both resting and dividing cells; therefore, at least 2 mechanisms are thought to be involved in its activity.

In dividing cells, cladribine is believed to be incorporated into DNA in its triphosphate form after phosphorylation by dCK. Cladribine appears in much higher concentrations within blood cells than in blood plasma (see section 2.2.1) and its cytotoxic effects on leukaemic cells correlate with the efficiency of its transport across the cell membrane.^[11] Within cells, it is phosphorylated by dCK and dephosphorylated by 5-NT; thus, it is not surprising that hairy cell leukaemia (HCL) and chronic lymphocytic leukaemia (CLL) cells from patients with leukaemia who responded to cladribine exhibited higher dCK ($p < 0.01$) and lower 5-NT ($p < 0.05$) levels than those from non-responders.^[12] Cladribine is resistant to adenosine deaminase, so phosphorylated forms of the drug accumulate within cells; 80% of a radiolabelled dose was identified as cladribine monophosphate and 10% as the triphosphate in human tonsillar lymphocytes *in vitro*.^[13] Incorporation of cladribine triphosphate into the DNA of dividing cells appears to arrest cell division.^[6]

In resting cells, cladribine is believed to induce apoptosis, or programmed cell death. DNA fragmentation is known to occur in a dose-related manner when cells from patients with CLL are exposed to cladribine *in vitro*.^[14] Cladribine also appears to induce expression of the p53 protein and its downstream target WAF1/CIP1 protein, which have been implicated in the apoptosis response to DNA damage.^[15] Apoptosis has also been measured in peripheral blood cells from 3 patients with HCL before and after intravenous cladribine (0.09 mg/kg/day infused for 7 days),^[16] rising from 2 to 3.4% at baseline to 20 to 32% after 5 to 14 days.

Table I. Effects of cladribine (CdA) on blood cell counts in patients with multiple sclerosis of the chronic progressive (CPMS) or relapsing-remitting (RRMS) forms

Parameter	Scripps IV CPMS (n = 29; 30mo observation) ^[19-21]	Scripps SC RRMS (n = ?; 10mo observation) ^[20]	Polish SC or PO RRMS (n = 11; 18mo observation) ^[22]	Polish SC RRMS (n = 90; ≈18mo observation) ^[23]
Dosage	CdA 0.087-0.1 mg/kg/day IV × 7 days q1mo × 4mo	CdA 0.07 mg/kg/day SC × 5 days q1mo × 6mo	CdA 5 mg/day SC or 10 mg/day PO × 5 days q1mo × 6mo, plus 1 or 2 additional courses at 3mo or 6mo intervals in some patients	CdA 5mg od SC × 5 days q1mo × 6mo; then 5mg od × 5 day 3mo later
Lymphocytes	Prolonged profound lymphopenia (especially of CD4+ cells) affecting both T (CD3+) and B (CD19+) cells; decreased CD4+/CD8+ ratio	Prolonged profound lymphopenia	Prolonged and profound decrease (from ≈2.5 × 10 ⁹ to 1 × 10 ⁹ cells/L), no correlation between decrease at 6mo and CdA dosage	Decrease to one-third of original counts
Monocytes	Acute transient monocytopenia	?	?	?
Granulocytes	Modest decrease	?	Little mean change (small decrease at 18mo)	'Not reduced significantly'
Haemoglobin	Modest decrease	Modest decrease	No change	?
Cell size	Prolonged macrocytosis	No macrocytosis	Slight macrocytosis in 'some patients', change in average MCV NS except at 18mo	'Some macrocytosis'
Platelets	Sharp decrease in counts for 6mo, nadir at 8mo, counts were <100 × 10 ⁹ cells/L in 7 of 29 patients (24%)	Variable platelet counts, no major change from baseline at 10mo	Decrease, but none <100 × 10 ⁹ cells/L	'Mild' thrombocytopenia 'of no clinical significance'

Abbreviations and symbol: IV = intravenous; MCV = mean corpuscular volume; NS = not statistically significant; od = once daily; PO = oral; q1mo = every month; SC = subcutaneous; ? = not reported.

Additional *in vitro* effects that may contribute to the mechanisms of action of cladribine include modification of the activity of DNA polymerase^[17,18] and ribonucleotide reductase^[18] and induction of dCK activity.^[13] For further discussion of the mechanism of activity of cladribine, see the review by Bryson and Sorkin.^[6]

2.1.2 Effects in Patients with Multiple Sclerosis

Cladribine has a clear profile of effects on lymphocytes and other blood cell counts in patients with MS (table I).

A marked and sustained reduction in lymphocyte counts appears to occur regardless of the total cladribine dose, type of MS or route of drug administration. In 4 trials (1 in patients with CPMS and 3 in patients with RRMS),^[20-23] subcutaneous, oral or intravenous cladribine use was associated with reductions in lymphocyte counts to ≈1 × 10⁹ cells/L or to at least one-half and up to one-third of base-

line counts, and these reductions lasted throughout the 10- to 30-month observation periods.

Effects of cladribine on other haematological parameters (e.g. platelet counts, cell size) appear to be related to the total dose and/or exposure period. They are greatest in patients with CPMS who received total doses of 2.8 mg/kg as 7-day intravenous courses (table I).^[20-22] The lesser effects seen in studies of patients with RRMS are not thought to be related to the disease type or the route of administration, but to the lower dosages (0.07 mg/kg or 5mg once daily subcutaneously or 10mg once daily orally) and the shorter courses (5 vs 7 days) adopted in the RRMS trials. Indeed, although thrombocytopenia and prolonged macrocytosis occurred with the higher total dose (2.8 mg/kg) in the patients with CPMS, only modest effects on platelet counts and cell size were observed in patients with RRMS receiving lower total doses (2.1

mg/kg) or lower daily dosages for shorter courses (5mg subcutaneously or 10mg orally for 5 days).

Little or no effect was seen on mean granulocyte counts or mean haemoglobin levels in these studies (table I). Monocytopenia was reported in the intravenous study, but was not discussed in reports of the other trials. For a discussion of other adverse effects of cladribine, see section 4.

2.2 Pharmacokinetics

As yet, no pharmacokinetic studies of cladribine have been conducted in patients with MS, but the kinetics of the drug are well studied in patients with haematological malignancies and solid tumours. Most of the pharmacokinetic research has been conducted in Sweden, and the kinetics of cladribine have been reviewed recently by Liliemark.^[24] An overview of cladribine pharmacokinetics based on the review of Liliemark is presented in table II.

The only commercially available form of cladribine is an intravenous injectable solution (1

mg/ml in normal sodium chloride and phosphate buffer),^[26,27] but the kinetics of the drug have been tested after intravenous, oral, subcutaneous and rectal administration. Other solutions have been prepared for subcutaneous administration (buffered 2.5 mg/ml at pH 7.4) or oral use (isotonic 1 mg/ml),^[22] and the drug has been formulated into enteric-coated capsules for oral testing.^[28] Although the kinetics of the drug after oral and rectal administration have been examined in patients with malignancies^[24] and the oral drug has been tested in clinical trials of patients with MS,^[22] bioavailability of these 2 forms is low ($\leq 51\%$ oral; $\approx 20\%$ rectal) and variable, so their use in patients with MS is not generally recommended (see section 5). Also, although originally used as a continuous 24-hour intravenous infusion, intravenous cladribine is now usually administered to patients with MS as 2-hour infusions once daily or as subcutaneous injections; these regimens/routes appear to result in pharmacokinetics and efficacy similar to those seen with use of the intravenous route.^[24]

2.2.1 Absorption and Distribution

Having no local tissue toxicity and 100% bioavailability, cladribine is suitable for administration as a subcutaneous injection.^[24] Variability in the area under the plasma concentration-time curve (AUC) is high between individuals, but is similar after oral and intravenous administration (coefficient of variation 38 vs 36%).^[24] Oral cladribine has low (37 to 51%) bioavailability. Food slowed and reduced oral absorption of cladribine. Although cladribine is unstable at low pH, oral bioavailability was not substantially increased by raising stomach pH with omeprazole.^[24]

Cladribine has a short distribution half-life of 8 to 11.9 hours and is widely distributed in the body cells, with a steady-state volume of distribution of up to 368 L/m². Concentrations of the drug and its nucleotides within cells are several hundred times higher than concentrations of the parent drug in plasma, but cannot be predicted by plasma concentrations. Cladribine and its metabolites are also retained in leukaemic cells, with a half-life of up to 30 hours, making the drug suitable for intermittent

Table II. Overview of cladribine pharmacokinetic parameters in adult patients with haematological malignancies (data from the review by Liliemark^[24] unless otherwise noted)

Parameter	Route		
	IV	SC	PO
F (%)		100	37-51
C _{max} (nmol/L)	142 after 2h 0.12 mg/kg infusion	268 after 0.12 mg/kg	165 after 0.24 mg/kg
t _{1/2α} (min)	8-11.9		
t _{1/2β} (h)	0.7-1.5		
t _{1/2γ} (h)	5.7-13.4		
V _{ss} (L/m ²)	54-368		
CL (L/h/m ²)	26-45		
CSF : plasma concentration ratio	0.25		
PB (%) ^[25]	Patients with haematological malignancies: 25 Healthy volunteers: 21.1 Human serum albumin <i>in vitro</i> : 24.3		

Abbreviations: CL = clearance; C_{max} = peak plasma concentration; F = bioavailability; IV = intravenous; PB = plasma protein binding; PO = oral; SC = subcutaneous; t_{1/2α} = distribution half-life; t_{1/2β} = elimination half-life; t_{1/2γ} = terminal elimination half-life; V_{ss} = volume of distribution at steady-state.

rather than continuous administration. Cladribine also distributes to the CSF, and although concentrations are lower there than in the plasma, the time course of CSF pharmacokinetics is roughly similar to that in plasma.^[24]

2.2.2 Metabolism and Excretion

Much of an orally administered dose may be deglycosylated to chloroadenine before absorption, resulting in the lower systemic availability of oral than intravenous cladribine.^[29] Chloroadenine is a major inactive catabolite of cladribine; its AUC is similar to that of cladribine after intravenous administration of 5 mg/m² (530 vs 508 nmol/L · h), but it has a 4.4-fold greater AUC than cladribine after oral administration (1863 vs 423 nmol/L · h).^[29]

Renal clearance is 51% of total systemic clearance of cladribine.^[24] 21 to 32% of an intravenously administered cladribine dose was excreted in the urine within 24 hours as unchanged drug^[24] and <10% was excreted as chloroadenine.^[24,29]

There are no data on the pharmacokinetics of cladribine in patients with impaired renal or hepatic function.

3. Therapeutic Potential in Multiple Sclerosis

The results of 2 pilot studies suggested that patients with CPMS^[30,31] and RRMS^[32,33] might benefit from cladribine treatment and that benefits may be due to immunological mechanisms. In 4 patients with clinically or laboratory-supported definite CPMS of ≥2 years' duration, cladribine 0.087 mg/kg/day intravenously for 7 days once a month for 6 months (total cumulative dose 3.7 mg/kg) resulted in reported improvements in clinical manifestations of the disease (assessed using the SNRS) and the disappearance of oligoclonal bands from the CSF.^[30,31] In 10 patients with RRMS and 'seemingly irreversible clinical deficits' on the EDSS, cladribine 5 mg/day subcutaneously or 10 mg/day orally was administered for 5 days once monthly for 6 months followed by 2 additional courses at 3-month intervals.^[32,33] The number of relapses was unchanged in 3 patients and reduced

markedly in the other 7, and EDSS scores decreased from a mean of 4.3 at baseline to 2.4 after 15 months' observation before gradually returning to baseline by 24 months.^[33]

None of the published reports of studies examined in this review differentiated between patients with primary progressive or secondary progressive forms of CPMS. To the extent that it is known, this information should be provided in reports of future clinical trials.

Additional and longer term trials examined different cladribine dosage schedules versus placebo in patients with confirmed CPMS or RRMS (see table III for study design details), and one retreatment study is also under way (results unavailable). Major study end-points were neurological functioning, MRI evidence of CNS lesions and clinical relapse. For effects of cladribine on haematological end-points, see section 2.1.2.

The EDSS and SNRS are semiquantitative scales that were used to test neurological functioning. In general, higher SNRS and lower EDSS scores indicate better functioning. EDSS and SNRS scores may not correlate in individual patients.^[39] The SNRS tends to show more gradual changes in disease course, and in a sample of 48 patients with CPMS it was nearly normally distributed about a mean of ≈70. The EDSS shows more abrupt changes, and, in the same sample of patients, exhibited bimodal distribution with modes of 3.5 and 6 to 6.5.^[39] MRI techniques can determine the extent of MS lesions in the CNS and the frequency of new disease activity, both of which assist prediction of the clinical course of the disease.^[40] In particular, gadolinium-enhanced MRI, which was used in studies examined in this review, may be up to 10 times more sensitive as a marker of disease activity than clinical data.^[40] In clinical trials, however, effects of drugs used to treat MS may be seen on MRI where no change may be seen in clinical findings.^[41] Thus, once it has been used to show the effects of agents in pilot studies, MRI is best kept for use only as a secondary end-point in controlled clinical trials.

Table III. Design of cladribine (CdA) clinical trials in patients with multiple sclerosis

Trial and reference	No. of patients	Study design	Drug and dosage	Duration of study	End-points	Comments
Chronic progressive multiple sclerosis (CPMS)						
Scripps pilot ^[30,34]	4	nr, nb, nc	CdA 0.087 mg/kg/day IV × 7 days q1mo × 6mo	6mo	Clinical manifestations CSF IgG	
Scripps 2-year CPMS ^[19,20,35]	51	r, db, pc, co ^a then 6mo nb; patients in initial PL vs CdA groups matched for disease severity	<i>Initial cladribine group:</i> CdA 0.1 mg/kg/day IV × 7 days q1mo × 4mo in year 1 then PL in year 2 <i>OR</i> <i>Initial placebo:</i> PL in year 1 then CdA 0.1 mg/kg/day IV × 7 days q1mo × 1mo, then 0.05 mg/kg/day IV × 7 days q1mo × 2mo in year 2 ^a	2.5y	EDSS SNRS MRI	6mo-20y illness duration at entry; also examined haematology (Beutler et al., ^[20,21] see section 2.1.2)
Scripps CPMS retreatment ^[34]	?	≥sb	CdA 0.05 mg/kg/day SC × 5 days q1mo × 4mo	?	?	Study is ongoing
Multicentre North American CPMS ^[34,36]	159	r, pc, pg, db	CdA 0.07 mg/kg/day SC × 5 days q1mo × 2mo (total dose 0.7 mg/kg) <i>OR</i> CdA 0.07 mg/kg/day SC × 5 days q1mo × 6mo (total dose 2.1 mg/kg) <i>OR</i> PL	1y	EDSS SNRS MRI	Full final results not published
Relapsing-remitting multiple sclerosis (RRMS)						
Polish RRMS pilot ^[32,33]	10	nr, nb	CdA 5mg SC × 5 days q1mo × 6 courses <i>OR</i> CdA 10mg PO × 5 days q1mo × 6 courses, then 2 further courses at 3mo intervals	2y	EDSS Relapse rate MRI	Mean 1.8 relapses per year at entry; also examined haematology (Grieb et al., ^[22] see section 2.1.2)
Polish double-blind RRMS ^[23,32,37]	90	r, db, pg	CdA 5mg SC × 5 days q1mo × 6mo; plus 1 further course 3mo later <i>OR</i> PL	30mo	EDSS Relapse rate	Study is ongoing; final results not published
Scripps 2-year RRMS ^[38]	50	r, db, pg	CdA 0.07 mg/kg/day SC × 5 days q1mo × 6mo <i>OR</i> PL	2y	EDSS SNRS MRI Relapse rate	

a Crossover took place after 1 year; patients receiving cladribine in year 2 (initial placebo group) were given a lower total dose (1.4 mg/kg) than those receiving it in year 1 (2.8 mg/kg, initial cladribine group).

Abbreviations: co = crossover; db = double-blind; EDSS = Kurtzke extended disability status scale; IV = intravenous; MRI = magnetic resonance imaging; nb = nonblind; nc = noncomparative; nr = nonrandomised; pc = placebo-controlled; pg = parallel group; PL = placebo; PO = oral; qxmo = every x months; r = randomised; SC = subcutaneous; SNRS = Scripps neurological rating scale; ≥sb = at least single-blind (details of blinding not reported).

Guidelines for the design of studies of MS therapies recommend placebo controls, randomisation, investigator blinding and controls for or consideration of the severity of disability, type and duration of disease and adequate study size and duration.^[42] Investigator blinding is an important design measure, since nonblind evaluation of EDSS and other neurological function tests is a known source of bias in studies.^[40] Considerations for study dura-

tion and sample size must account for the slow progression or remitting nature of the disease. Studies in patients with CPMS must be of sufficient duration to show a deterioration of function in untreated patients, and randomised studies must enrol a large enough number of patients to be able to detect a difference between treatments.^[40] Detection of differences in neurological function, in particular, may be complicated by the fact that the most

widely used outcome measure, the EDSS, is not particularly sensitive to minor changes in disease severity.^[40]

Published information about the design of comparative cladribine clinical trials suggests that most had appropriate study designs, despite the lack of detail about some trials (design details have been published in full only for the Scripps 2-year CPMS study).^[19,20,35] Although pilot studies were non-blind, nonrandomised and of short duration, all comparative trials used randomisation, placebo control and both investigator and patient blinding. Most studies followed patients for at least 2 years and appeared to have enrolled adequate numbers of patients (although some studies are still ongoing). However, the North American multicentre study may have enrolled too few patients and/or followed patients for too short a duration (see section 6).

3.1 Effects on Neurological Function

3.1.1 Chronic Progressive Multiple Sclerosis

A clear effect of cladribine on neurological functioning was seen in the Scripps 2-year CPMS study in 48 patients matched for disease severity,^[19] but no effect was observed in the 1-year multicentre North American trial that randomised 159 patients to receive cladribine or placebo.^[36] For a discussion of the effects of methodological factors on the results of these studies, see section 6.

In the Scripps 2-year CPMS study, cladribine produced modest improvements in EDSS and SNRS scores that were sustained for 18 to 24 months, whereas placebo was associated with deteriorating neurological functioning. In addition, both the time-to-improvement and time-to-failure (indicated by changes of 1 EDSS or 10 SNRS points) showed statistically significant benefits of cladribine.^[19]

EDSS scores in the group randomised to receive cladribine in the first year of study (initial cladribine group) improved from 4.8 at baseline to 4.4 at 13 months, with deterioration from baseline values occurring only after 18 months. In the group receiving placebo in year 1 (initial placebo group),

EDSS scores increased from 4.7 at baseline to 5.6 at month 13; low-dose cladribine therapy begun in this group in month 13 produced an improvement that peaked at EDSS scores of 5.1 at month 19 before function deteriorated again.^[19] Changes in EDSS from baseline in both patient groups are shown in figure 1a.

SNRS scores (fig. 1b) showed more sustained improvements with cladribine than were seen in EDSS scores in the 2-year Scripps CPMS study. A score of 69.6 at baseline increased to a peak of 75.7 at 18 months in the initial cladribine group and did not return to baseline until 30 months. However, in the initial placebo group, SNRS scores decreased from 68.3 to 62.1 at 12 months, then increased after the introduction of cladribine to 70.8 at month 19, after which they began a gradual decline.^[19]

Investigators in the Scripps 2-year CPMS study also noted a less durable therapeutic effect of the better-tolerated lower total dose of 1.4 mg/kg than of the higher 2.8 mg/kg dose.^[19] However, although there was only a minor 1.292 point difference in SNRS scores at the start of cladribine therapy, EDSS scores had already deteriorated by 0.7292 points when the initial placebo group began the lower cladribine dose in the second year of the study. Thus, without a direct comparison controlling for disease severity at the time of drug initiation, it is difficult to know if differences in durability of therapeutic effects are solely a sign of a dose-response relationship or may be attributable to disease factors.

It is also interesting that the improvements seen in neurological functioning in the Scripps 2-year CPMS study began to erode $\approx$ 1 year after the start of treatment, long before the CD4+ counts or CD4+ : CD8+ ratios began to increase (after $\approx$ 18 months).^[19] However, in the multicentre North American study (n = 159), neither cladribine nor placebo recipients exhibited signs of progression on either EDSS or SNRS scales, and no differences were seen between the treatment groups. The lack of difference was thought to be due to unexpectedly good results in the placebo group,^[36] but may be

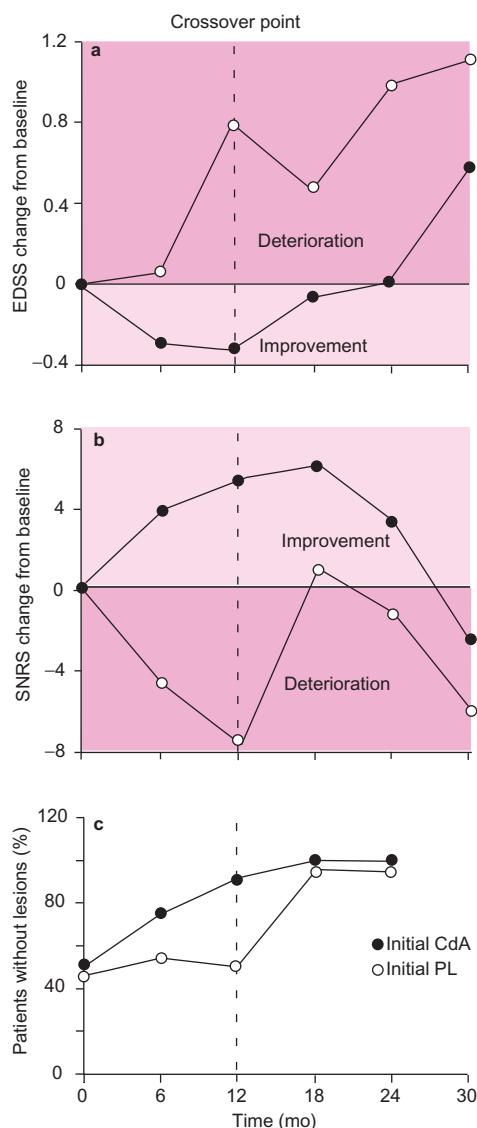


Fig. 1. Effect of cladribine (CdA) on neurological functioning and CNS lesions in patients with chronic progressive multiple sclerosis (CPMS) in the Scripps 2-year CPMS study.^[19] 24 patients received intravenous CdA 0.1 mg/kg/day for 7 days for 4 monthly courses in year 1 then intravenous placebo (PL) in the second year (initial CdA group). Another 24 patients matched for disease severity received intravenous PL in the first year and in the second year received intravenous CdA 0.1 mg/kg/day for 7 days in the first month, then 0.05 mg/kg/day for 7 days once monthly for 2 more courses (initial PL group); (a) change in Kurtzke extended disability status scale (EDSS) from baseline; (b) change in Scripps neurological rating scale (SNRS) from baseline; (c) percentage of patients without CNS lesions detected by gadolinium-enhanced magnetic resonance imaging.

attributable to inadequate study duration or sample size (see section 6).

3.1.2 Relapsing-Remitting Multiple Sclerosis

Although neurological functioning improved in more and worsened in fewer patients with RRMS receiving cladribine than placebo, the clinical significance of this finding is doubtful. In an interim assessment of the Polish double-blind study, after 30 months of observation, 52% of 31 cladribine recipients showed improved neurological function and only 10% worsened by 1 EDSS point, vs 25 and 18% of 40 patients receiving placebo. Patients receiving cladribine had EDSS scores of 3.61 at entry which reduced to a statistically significant extent by 0.63 points at 30 months. In contrast, the placebo group score of 3.91 reduced nonsignificantly by 0.13 points in the same time.^[32] However, changes of less than 1 point in EDSS scores are probably not clinically significant, so these changes suggest there is little real difference between groups. As yet, no published neurological function data are available from the Scripps 2-year study in patients with RRMS.

3.2 Effects on CNS Lesions and Relapse

3.2.1 Chronic Progressive Multiple Sclerosis

The number of patients with CNS lesions present on gadolinium-enhanced MRI decreased by up to 100% following cladribine therapy in the Scripps 2-year study, but did not change during placebo use (fig. 1c).

In addition, it appears that both the high (2.8 mg/kg, i.e. initial cladribine) and low (1.4 mg/kg, i.e. initial placebo) total doses of cladribine reduced the number of patients with gadolinium-enhanced lesions in the Scripps 2-year CPMS study. Furthermore, the effects of the initial high-dose regimen on MRI persisted to the end of the 30-month observation period.^[19]

In the multicentre North American study, both cladribine dosages were associated with >90% suppression of gadolinium-enhanced lesions.^[36] Results for placebo were not published.

Relapse was not examined in patients with CPMS.

3.2.2 Relapsing-Remitting Multiple Sclerosis

CNS lesions appeared to regress in the Scripps 2-year RRMS study, with a reduction in the number of patients with CNS lesions present on gadolinium-enhanced MRI (reported in an abstract).^[38] These lesions were said to be 'virtually absent' in patients receiving cladribine, while still present in placebo recipients. In addition, the frequency and severity of relapses was reported to be significantly reduced in patients receiving cladribine. No further published details are available.

Published MRI results of the Polish double-blind study cover only 83 patients for an unspecified time from the start of treatment.^[37] Although it was reported that the number of new plaques detected on MRI were twice as great in the placebo as the cladribine group (8 vs 4), the numbers were too small for statistical analysis.

4. Tolerability

Dose-limiting myelosuppression, culture-negative fever and infection in the weeks following treatment are the most common adverse events associated with cladribine in patients with haematological malignancies, in whom the drug has been most intensively studied.^[43] Because patients are often unaware of the mostly haematological adverse events seen with cladribine,^[44] careful monitoring is essential.

4.1 Haematological Events

Bone marrow suppression has been observed in patients with MS receiving high dosages of cladribine; because of this, the maximum tolerated dose is 0.1 mg/kg/day for 7 days every 28 days. Seven of 24 patients with CPMS receiving a total intravenous cladribine dose of 2.8 mg/kg in the Scripps 2-year CPMS study had thrombocytopenia ($<100 \times 10^9$ cells/L), compared with only 1 of 24 receiving a lower 1.4 mg/kg total dose.^[20] The multicentre North American trial in patients with CPMS also reported that thrombocytopenia was less common at lower dosages.^[36] The maximum tolerated dose in 7-day courses of cladribine every 28 days was defined in a dose-escalation study in

21 patients with nonhaematological malignancies.^[45] Myelotoxicity occurred in 1 of 7 patients receiving cladribine 0.1 mg/kg/day, compared with 4 of 11 patients receiving 0.15 mg/kg/day and all 3 patients receiving 0.2 mg/kg/day.^[45] A total of 18 7-day courses could be given in this trial, with a total dosage of ≤ 12.5 mg/kg. For a discussion of the effects of the drug on other haematological parameters, see section 2.1.2.

Other adverse haematological effects occurred with cladribine, but may have been related to concomitant use of other marrow-suppressant drugs. Two of 29 patients receiving cladribine in the Scripps intravenous trial^[21,22] developed aplastic anaemia and required transfusions of erythrocytes and platelets. However, 1 patient had received chlorambucil 950mg in the previous year and the other had received carbamazepine and phenytoin before or during cladribine use. In contrast, no transfusions were needed in any of 11 patients in the Polish trial^[22] (results on these end-points are unavailable for the Scripps RRMS trial).^[20]

4.2 Fever, Neutropenia and Infection

According to the manufacturer's prescribing information, approximately two-thirds of patients with HCL experienced fever following cladribine administration, but only one-third of those fevers were associated with documented infection.^[26] Fever has not been reported as an adverse event during cladribine therapy of MS, but further examination of this event in MS patients is needed.

Neutropenia has been clearly associated with the cladribine AUC in patients with solid tumours,^[46] which suggests that the use of lower doses and shorter courses may reduce the incidence of this adverse event.

Infections were reported in patients with MS receiving cladribine in clinical trials. Four of 48 (8%) patients with CPMS in the Scripps 2-year intravenous trial experienced herpes zoster that responded to oral aciclovir, and 1 other patient had fatal fulminating hepatitis B (thought not to be related to treatment).^[20] One additional patient examined by the Scripps group developed peritoneal coccidi-

oidalmycosis, which responded well to therapy (E. Beutler, personal communication). In the Polish RRMS study, several patients were reported to have 'increased frequency of upper respiratory tract infections', especially during the last 6 months of observation (1 had recurrent infections); all infections responded to standard antibacterial therapy.^[22] Studies in patients with haematological malignancies suggest that opportunistic infections are most common 'in the immediate post-treatment period'.^[30]

4.3 Other Events

Neurotoxicity has been reported in patients receiving cladribine at doses 4 to 9 times those usually recommended for the treatment of HCL, but this event is rare at usual HCL treatment doses^[26] and has not been reported in patients with MS. No nephrotoxicity has been observed at the usual dosage used to treat HCL or MS.^[27]

4.4 Long Term Follow-Up

Unpublished data on ≈ 35 patients treated with total cladribine doses of 2.8 mg/kg or more prior to 1992 have been gathered by the Scripps group (E. Beutler, personal communication). In 2 patients who developed persistent mild thrombocytopenia, bone marrow examination uncovered myelodysplastic changes in their marrow, including a deletion from the long arm chromosome 20 in some mitoses. Both patients were reported to be haematologically stable, requiring no therapy. Complicating the assessment of this finding is a family history of development of a myelodysplastic syndrome, occurring in the mother of 1 of these patients. Beutler reports that, because myelodysplasia is a premalignant disorder, the incidence of malignancies in all patients who received cladribine to treat MS at Scripps was analysed. In the small cohort examined, the incidence of malignancy was reported to be 'slightly under expectation' (E. Beutler, personal communication).

5. Dosage and Administration

There are no current manufacturer recommendations for the use of cladribine in patients with MS. Guidelines given here are based on clinical trials conducted in patients with MS and the manufacturer's recommendations for use of the drug in patients with haematological malignancies.

It has been recommended that all patients with MS who have received cladribine therapy and are being considered for subsequent treatment courses should satisfy the following criteria:^[34]

- platelet counts of $\geq 200 \times 10^9$ cells/L *or* 150 to 200×10^9 cells/L and $>50\%$ of previous pretreatment platelet counts *or* 125 to 150×10^9 cells/L and $>80\%$ of previous pretreatment platelet counts
- absolute granulocyte counts $>10^9$ cells/L
- haemoglobin level reduced by no more than 15 g/L from previous pretreatment level *or* by no more than 30 g/L from baseline.

It is also recommended that cladribine recipients be monitored during therapy and for up to 8 weeks after treatment for the following:^[26]

- haematological changes (platelet count, absolute neutrophil count, haemoglobin)
- signs of neurological toxicity (which is rare in patients with haematological malignancies and has not been reported in patients with MS)
- deterioration in renal and hepatic function
- fever, the cause of which should be investigated.

The use of cladribine should be avoided in patients with signs of active infection or haematological disorders.

The maximum recommended cladribine dosage for patients with nonhaematological malignancies was 0.1 mg/kg/day,^[45] with myelosuppression being the major dose-limiting toxicity. The usual dosage for patients with active HCL is one 7-day course of 0.09 mg/kg/day given as a continuous intravenous infusion.^[26] In patients with MS, the following cladribine regimens have been or continue to be tested:

- 0.05 mg/kg/day subcutaneously for 5 days each month for 4 months

- 0.07 mg/kg/day subcutaneously for 5 days each month for 2 or 6 months
- 5 mg/day subcutaneously for 5 days each month for 6 months.

Subcutaneous administration has superseded previously used intravenous infusions, being easier to use and providing similar efficacy. The use of regimens containing low total dosages is now more common in clinical studies. Oral cladribine has been used effectively in 1 published clinical trial at twice the subcutaneous daily dose.^[22] However, the risk of patients absorbing the entire dose and experiencing bone marrow suppression is thought by some^[20] to be too great to warrant use of cladribine by the oral route. Therefore, oral use of cladribine should be restricted to patients who may benefit from use of the drug but for whom the use of injectable dosage forms may be unacceptable. Rectal use of cladribine is not recommended (see section 2.2).

Cladribine is not recommended for women who are pregnant, breast-feeding or at risk of becoming pregnant. Caution is advised when cladribine is used in patients with renal or hepatic insufficiency, since its use in these patients has not been studied. Although there are no known drug interactions with cladribine, caution is recommended when the drug is administered before, after or with other drugs that may cause myelosuppression or immunosuppression.^[26]

6. Place of Cladribine in the Management of Multiple Sclerosis

It appears that cladribine may be able to slow or temporarily reverse neurological deterioration and reduce the number of MRI-detected CNS lesions in patients with either CPMS or RRMS at high (2.8 mg/kg) and low (1.4 mg/kg) dosages. In the Scripps CPMS 2-year study, EDSS and SNRS scores improved during the first 13 months with high dose cladribine and appeared to persist beyond baseline for up to 2 years,^[19] which is similar to the duration of effect of cladribine on lymphocytes in the same study.^[21] It also appears that dose-limiting bone marrow suppression can be min-

imised through the use of cladribine dosages not exceeding 0.07 mg/kg/day. Although patients may experience opportunistic infections during cladribine therapy of MS, these tended to respond to appropriate therapy. In addition, cladribine may now be administered subcutaneously and in shorter (5-day) courses, which are more convenient than the 7-day intravenous regimens.

However, to date, details of only 2 clinical trials have been published in full; information on other trials is available mainly as abstracts. This leaves gaps in the knowledge of the effects of cladribine.

Furthermore, the results of CPMS studies are conflicting. Patients receiving placebo in the multicentre North American study showed no neurological progression, which is unusual in patients selected for having evidence of progressive disease, and it has been suggested that patients in the Scripps 2-year CPMS study progressed more rapidly than is normally expected.^[47] Patients receiving initial placebo in the latter trial were carefully matched with recipients of initial cladribine for similar disease severity, then each matched pair was randomised.^[48] In contrast, in the shorter multicentre North American study, control for variation in disease severity was accomplished only by randomisation to cladribine or placebo groups.^[36] Thus, despite enrolling more patients than the Scripps 2-year study (48 patients), the 1-year multicentre study may have had too small a patient sample (159 patients) or too short a duration to detect differences between treatment regimens in unmatched patients.^[36]

In addition, CPMS studies have not clearly differentiated between patients with primary and secondary forms of the disease, which differ in their characteristics on MRI and in the speed of progression.^[3] This information should be included in future study reports. Cladribine also produced clear reductions in numbers of MRI-detected lesions in most clinical trials, but improvements in neurological functioning did not always accompany these changes, a finding that supports the current view that MRI should be used only as a secondary outcome measure in MS clinical trials.^[41] Thus, al-

Table IV. Comparison of key features of cladribine and other immune-based therapies for multiple sclerosis

Feature	Cladribine	Interferon- β 1a ^[50,51]	Interferon- β 1b ^[52]	Glatiramer acetate (copolymer-1) ^[53]
Mechanism of action	Selective depletion of lymphocytes; $\downarrow$ CD4+/CD8+ ratio	$\downarrow$ T cell surface activation markers $\downarrow$ CNS interleukin-10	Improves suppressor CD8+ T cell function $\downarrow$ T cell activation	Inhibits binding of myelin proteins to major histocompatibility complex
Route of administration	SC optimal, but IV and PO viable	IM or SC	SC	SC
Dose	5-day SC courses of 0.05-0.07 mg/kg/day or 5 mg/day at monthly intervals for 2-6 courses	30 μ g IM once weekly or 12-44 μ g 3 $\times$ weekly SC	1.6 or 8 MIU SC every other day	20mg SC once daily
Adverse events	Bone marrow suppression (dose-dependent) Fever Infection	Flu-like symptoms Headache Nausea Fever	Flu-like symptoms Injection site reactions	Injection site reactions Systemic reaction (flushing, chest tightness, dyspnoea, palpitations, anxiety)
Chronic progressive multiple sclerosis				
Results	Improved SNRS and maintained EDSS scores or produced no changes; reduced CNS lesions	No published results	No published results	Inconclusive results
Relapsing-remitting multiple sclerosis				
EDSS	Interim results suggest slowed progression in some patients	Significantly slows confirmed progression	Little effect on progression	Nonsignificant tendency to slow confirmed progression
CNS lesions	Improved	Improved	Improved	Improved
Relapse	Reduced	Reduced	Reduced	Reduced

Abbreviations and symbols: EDSS = Kurtzke extended disability status scale; IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous; SNRS = Scripps neurological rating scale; $\downarrow$ = decreased.

though it is encouraging that MRI findings of CPMS studies indicated regression of CNS lesions during cladribine therapy, questions about study methods warrant caution in interpretation of results.

Given these considerations, longer term trials of cladribine in larger numbers of patients appear to be needed so that early results in CPMS and RRMS can be confirmed. There is still more to be learned about optimal cladribine dosages, ideal timing for retreatment and how cladribine compares with other agents used to treat MS. It may also be worth examining the potential for use of cladribine in combination with other agents used to treat MS.

With regard to comparisons, corticosteroids are a mainstay of treatment of acute exacerbations of MS. However, corticosteroids do not alter the usual course of the disease.^[49] In the 1990s, the approach

of considering MS as an autoimmune disease has resulted in several new therapies. A comparison between the key features of cladribine and interferons β 1a and β 1b and glatiramer acetate (copolymer-1) is presented in table IV.

Although all these agents act on lymphocytes, the nonselective lymphotoxic effects of cladribine may have the possible advantage of greater efficacy in patients with CPMS, but the disadvantage of dose-limiting myelotoxicity. To date, cladribine is the only one of these agents to have been shown to improve the course of CPMS (table IV); results from studies of other agents are either inconclusive or have yet to be published. For patients with RRMS, however, differences in efficacy between these agents cannot be discerned without direct comparative trials. Other factors may also play a role in the choice of therapy. Tolerability of these

agents and ability of patients or their caregivers to manage injectable therapy must be considered in management of the disease. Cost will be another consideration, but the lack of data on cost factors prevents speculation on this subject.

Thus, additional study is needed to determine whether cladribine will be useful in the management of patients with either chronic progressive or relapsing-remitting forms of multiple sclerosis. Its potential activity in this disease is based on the hypothesis that it acts by reducing the number of activated lymphocytes that can damage myelin. In patients with chronic progressive disease, it appears to result in temporary improvement or no change in neurological functioning and a reduction in CNS lesions as evinced by MRI. The few data available indicate that similar effects are also seen in patients with relapsing-remitting disease, in whom it may also reduce rates and severity of relapses. Ongoing and future studies are needed to confirm its efficacy, compare it with that of other available drugs and determine its optimal administration schedule and the optimal time for retreatment. If the preliminary results are confirmed, cladribine may come to be used to prevent or delay progression of multiple sclerosis in appropriately selected patients with chronic progressive or relapsing-remitting forms of this disease.

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