

Cladribine in the treatment of multiple sclerosis

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Treatment with cladribine leads to a preferential and sustained reduction in lymphocytes and monocytes, resulting in long-lasting depletion of CD4⁺ and CD8⁺ T cells. In the Phase III placebo-controlled trial in relapsing–remitting multiple sclerosis (the CLARITY study), oral cladribine at 96 weeks significantly reduced annual relapse rates by 54–57% compared with placebo. The risk of disability progression and brain lesion counts on MRI were also decreased. The therapy was well tolerated. The dosing regimen is convenient, but careful surveillance is still needed to detect unforeseen side effects. Until long-term safety data are available, the use of oral cladribine would primarily be as an escalating therapy in patients with breakthrough disease on IFN- β and glatiramer acetate.

Keywords: cladribine • lymphocyte depletion • multiple sclerosis
• oral immunosuppressive therapy

Multiple sclerosis (MS) is a chronic and debilitating autoimmune disorder of the CNS mainly affecting young adults [1], in which T and B lymphocytes are believed to play a major pathophysiological role in the inflammatory demyelinating attack [2–5]. The currently approved disease-modifying drugs (DMDs) for relapsing forms of MS (i.e., IFN- β , glatiramer acetate, mitoxantrone and natalizumab) are all parenteral immunomodulatory or immunosuppressant therapies that are either safe but moderately effective, or more effective but with safety and tolerability concerns that may limit their general utilization. Furthermore, parenteral administration may present relative or absolute barriers to acceptance of the therapy. Consequently, all the current therapies possess inherent factors that may affect treatment acceptance, adherence and long-term outcomes [6].

Hence, there is an urgent need of oral treatments with a favorable benefit-to-risk profile for the treatment of MS, and the present article evaluates whether cladribine possesses properties that may fulfill these requirements.

Mechanism of action

Cladribine (2-chloro-2'-deoxy- β -D-adenosine) also known as 2-CdA, is a synthetic deoxyadenosine analog with substitution of a hydrogen atom with chlorine at the 2-position of the purine ring (Figure 1). This substitution makes the nucleoside analog resistant to degradation by adenosine deaminase, an enzyme that metabolizes and clears the naturally occurring deoxynucleosides. Cladribine enters the cell via nucleoside transporter proteins. Inside the cell, cladribine is activated through three successive phosphorylations, the first of which is catalyzed by the enzyme deoxycytidine kinase [7,8]. Activated cladribine can be inactivated through dephosphorylation by the enzyme 5'-nucleotidase (5'-NTase). Compared with other cells, lymphocytes have a high concentration of deoxycytidine kinase and a low concentration of 5'-NTase, and, therefore, accumulate higher concentrations of the phosphorylated molecule, which becomes trapped inside the cell resulting in a preferential accumulation of phosphorylated, or activated, cladribine (Figure 2) [9].

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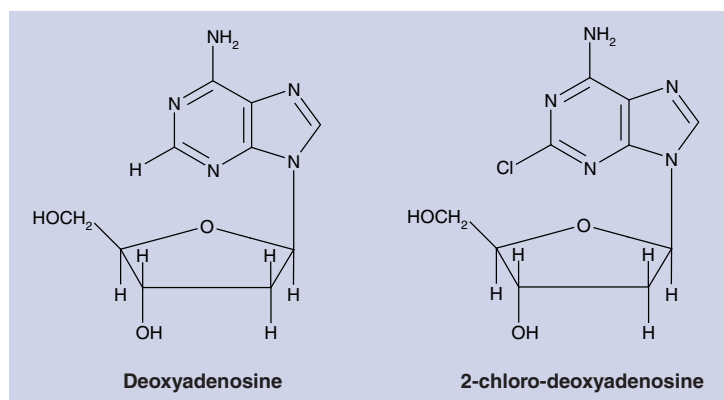


Figure 1. Cladribine.

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Treatment with cladribine leads to a preferential and sustained reduction in lymphocytes and monocytes, resulting in long-lasting depletion of CD4⁺ and CD8⁺ T cells. However, reductions in neutrophils, platelets and erythrocytes are modest and mean levels of these cells remain within the normal range throughout the period of treatment. The exact mechanism of action of cladribine in dividing and nondividing cells is still unknown, but its effect is immunosuppressive and has

been approved for the treatment of hairy cell leukemia since 1980 [10]. Furthermore, accumulation of active triphosphate deoxynucleotides (CdATPs) interferes with the DNA repair of single-stranded breaks, eventually resulting in cell death [11,12]. In dividing cells, CdATP can also be incorporated into the DNA, impairing transcription. Cladribine causes apoptosis through the caspase system where the cytochrome C and apoptotic protease-activating factor activate caspase-3 and damage DNA [13]. These cytotoxic mechanisms interfere with the synthesis and repair of DNA in both resting and dividing lymphocytes, providing effective immunosuppression, but raises concerns regarding the risk of secondary malignancy.

Furthermore, new data suggest that cladribine may be acting as a hypomethylating agent through its inhibition of S-adenylhomocysteine hydrolase. Specifically, it decreases DNA methylation by an effect on DNA methyltransferase. Work on a human leukemia cell line showed that cladribine inhibits global DNA methylation [14]. Studies on chronic lymphocytic leukemia suggest that DNA methylation levels are predictors of disease progression and treatment with cladribine revealed lower DNA methylation, which correlated with treatment response [15,16]. There is growing evidence that cladribine may have epigenetic properties by turning off oncogenic signaling [17]. Cladribine may also have more specific immunomodulatory effects on proinflammatory cells and cytokines. Chronic progressive MS patients treated with cladribine had statistically significant lower mean IL-2 levels after 12 months compared with baseline [18]. Reduced levels of CCL5 (RANTES) in the cerebrospinal fluid and serum have been found in patients treated with cladribine [19]. *In vitro* studies report that cladribine may modulate the secretion of cytokines by human T cells [20].

Pharmacokinetics

Available data are found in the initial studies in hairy cell leukemia patients with normal renal function. The drug is distributed widely throughout the body tissues, with 20% binding to plasma proteins. In the cerebrospinal fluid the concentration of cladribine is almost 25% of the plasma drug concentration [21]. Renal clearance amounts to 50% of the total clearance. Bioavailability seems to be the same regardless of the dosing regimen (continuous infusion in 24 h, subcutaneous bolus or 2 h bolus infusion), although only smaller study populations on leukemia have been published [22,23]. Comparing the 2-h bolus with the 24-h continuous infusion, the area under the curve was the same. Furthermore, more than 6 h after the bolus infusion, the concentration was the same as the 24-h steady state infusion [24,25].

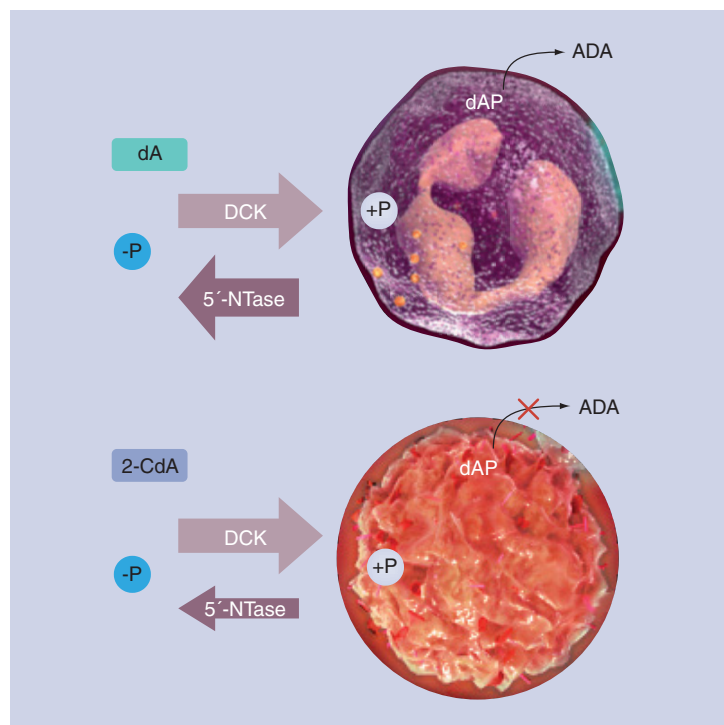


Figure 2. Mechanisms of action of cladribine.

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Trials of intravenous & subcutaneous administration of cladribine in MS

Trials of parenteral cladribine for relapsing and progressive MS were conducted at the Scripps Research Institute in the 1990s [26,27]. In 1999, Romine *et al.* published data on an 18 month placebo-controlled, randomized treatment of relapsing–remitting multiple sclerosis (RRMS) with cladribine 2.1 mg/kg subcutaneously or placebo [28]. On MRI, the number of gadolinium-enhancing lesions was significantly reduced in the cladribine-treated group compared with the placebo group at month 12 ($p = 0.0001$) and also at month 18 ($p = 0.02$). Clinically, a combined measure of the frequency and severity of relapses was significantly reduced in the cladribine group versus the placebo group at 12 months and was still reduced at 18 months ($p = 0.010$).

In another study on progressive MS, 159 patients with a median Expanded Disability Status Scale (EDSS) score of 6.0 were randomly assigned to receive cladribine at total doses of 0.7 or 2.1 mg/kg or placebo. Mean changes in disability on Kurtzke's EDSS [29] or Scripps Neurological Rating Scale (SNRS) [30] did not differ among the groups at the end of the 12-month double-blind phase [27,31]. These results led to speculations on the patient population that had a high median EDSS and 30% had primary progressive MS, which may be less sensitive to the anti-inflammatory effect of cladribine. The placebo-treated patients had a slower disease progression than anticipated and this resulted in an underpowered trial. The MRI findings were more compelling, as gadolinium-enhancing lesions were markedly reduced in both mean volume and number (>90%) in both the cladribine-treated groups compared with the placebo group ($p < 0.003$) [31].

A recent study of RRMS randomized 84 patients blindly to cladribine treatment (mean cumulative dose 2.45 mg/kg) in a double crossover design, with treatment periods of 1 year. One group of patients received cladribine in year 1 and placebo in year 2 and had a mean relapse-rate of 0.15 on cladribine and 0.42 in the following placebo year (relative difference 64%). The other group received treatment in the reversed order and the relapse rate was 0.61 in the first placebo year and 0.50 in the second cladribine treatment year (relative difference 18%). The mean EDSS remained stable [32].

Toxicity & tolerability of parenteral cladribine

Hematological malignancies have been treated with parenteral cladribine for more than 15 years revealing a generally safe short-term profile and predictable side effects [24]. Significant myelosuppression can give toxic symptoms, with higher doses leading to stem cell toxicity and infectious complications. Doses of 0.1 mg/kg/day for 7 consecutive days induced significant, although

transient, myelosuppression in most patients. The effects of the drug were cumulative, and in particular, patients with poor bone marrow reserve receiving repeated dosing have developed thrombocytopenia [33]. Doses two- to nine-times higher than the recommended dose of 0.1 mg/kg/day resulted in myelosuppression, fatal systemic infections, acute nephrotoxicity and polyneuropathy. In a dose-escalation Phase I study with 36 patients with relapsed acute myeloid leukemia, six patients developed severe sensorymotor peripheral neuropathy, regaining only some ambulatory function [34]. Neurological side effects were, however, not found in a study with similar dosing [35,36]. Myelosuppression as reflected by foci of bone marrow hypoplasia/aplasia was reported by Gillis *et al.* treating patients with hairy cell leukemia. Most patients had normal peripheral blood counts and after 7 years follow-up, the hypoplasia was not found to be predictive for the development of significant cytopenias. In general, long-term data were sparse so the clinical importance of these findings is unclear [37].

Two articles following patients after treatment with cladribine for chronic lymphoid leukemias ($n = 2014$) and hairy cell leukemia ($n = 350$) reported no increased risk for second malignancies [35,38]. However these safety reports may not necessarily apply to MS populations, and long-term clinical and laboratory monitoring are warranted.

In the early treatment trials conducted at the Scripps Research Institute, parenteral cladribine for MS was well tolerated [7,26,27]. Muscle weakness, hypertonia, purpura, rhinitis and ataxia occurred more frequently among cladribine-treated patients than in the placebo group. Upper respiratory tract infection, pharyngitis, back pain, arthralgia and skin disorders were more common in the cladribine 2.1 mg/kg group than in those receiving cladribine 0.7 mg/kg or placebo. The incidence of serious adverse events (herpes zoster cutaneous infections) was similar in patients receiving cladribine at doses of 0.7–2.1 mg/kg or placebo. All responded to standard antiviral therapy [27]. Reduced mean lymphocyte counts were found 4–6 weeks after therapy and remained low for at least 6–12 months [31,32]. The lymphocyte reduction was dose-dependent for patients receiving doses of 0.7–2.1 mg/kg. Analysis of lymphocyte subsets showed marked reductions in CD4⁺ T-cell counts lasting for at least 12 months and less marked for CD8⁺ T-cell counts. Mean B-cell counts decreased during the first 2–7 months of therapy but recovered to near baseline levels after 7 months. Natural killer cell counts decreased during the first months and rose to near baseline levels at 7 months. Two patients had transient thrombocytopenia (one receiving placebo and one cladribine) and one patient on cladribine had a single low neutrophil count (960/ μ l). There were no effects on hepatic, renal or serum chemistries [27]. In a recent study of 84 RRMS

patients treated subcutaneously with a mean cumulative dose of cladribine 2.45 mg/kg no serious adverse events were reported [32].

Studies in animals treated with cladribine have shown ocular and limb defects in mice and rabbits and also lumbar hernia in rats [39]. Data on human teratogenicity are lacking, but cladribine inhibits DNA synthesis and should, therefore, not be administered during pregnancy. One successful pregnancy has been reported in a patient treated for hairy cell leukemia. Interestingly, it had been speculated that the patient's use of oral contraceptive pills through her cladribine course might have helped to preserve her ovarian function [40]. In the Trial of Oral Cladribine for Relapsing MS (CLARITY) study two patients who had received oral cladribine delivered normal-term live infants [41].

Treatment of RRMS with cladribine tablets (CLARITY & CLARITY extension studies)

■ Patients & study design

The results of the Phase III, placebo-controlled CLARITY study were recently published [41]. A total of 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5 or 5.25 mg/kg of body weight) or placebo administered over 96 weeks, given in two or four short courses starting at week 1 and 5 for the first 48 weeks, and then in two short courses starting at week 48 and 52 (for a total of 8–20 days/year). Each course consisted of cladribine or placebo 10 mg tablets given once daily for the first 4–5 days of a 28-day period. Patients had a diagnosis of RRMS according to McDonald criteria [42], lesions on MRI consistent with Fazekas criteria [43] and had at least one relapse within 12 months before study entry, with a score of no more than 5.5 on the EDSS [29]. The demographics and clinical characteristics of the intention-to-treat population of 1326 patients were well-balanced across the three study groups. The mean age was 37.9–39.1 years (range 18–65 years); the mean disease duration was 7.9–9.3 years (range 0.3–42 years) and mean EDSS was 2.8–3.0. Almost one-third of patients had previously received disease-modifying therapy. Overall, 1184 patients (89.3%) completed the 96-week study (91.9% in the cladribine 3.5 mg group, 89.0% in the cladribine 5.25 mg group, and 87.0% in the placebo group). The primary end point was the rate of relapse at 96 weeks. Key clinical secondary end points were the proportion of patients who were relapse-free and the time to sustained progression of disability. Secondary MRI end points were the mean number of lesions per patient per scan at 96 weeks for gadolinium-enhancing T1-weighted lesions, active T2-weighted lesions and combined unique lesions (new gadolinium-enhancing T1-weighted lesions or new enlarging T2-weighted lesions) [41].

■ Efficacy

Treatment with cladribine tablets significantly reduced the annual relapse rates (0.14 for the group receiving 3.5 mg/kg and 0.15 for the 5.25 mg/kg versus 0.33 for the placebo group [relative reductions: 57.6 and 54.5%, respectively; $p < 0.001$]). A higher proportion of patients were relapse-free in the cladribine groups (79.7 and 78.9%, respectively) versus the placebo group (60.9%; $p < 0.001$ for both) and cladribine therapy was associated with a significantly lower risk of 3-month sustained disability (Table 1). The ultimate goal is to prevent the development of long-term sustained disability and it has, therefore, been noted that an end point of only 3 months for this observation is too short [44]. The authors have acknowledged this and data on 6 month confirmed disease progression is being obtained as part of an ongoing, exploratory, *post hoc* analysis. These clinical findings were underscored by the results of MRI of the brain. Patients in the cladribine 3.5 or 5.25 mg/kg groups had fewer lesions per patient per scan for: T1 gadolinium-enhancing lesions (mean 0.12 and 0.11 vs 0.91), active T2 lesions (mean 0.38 and 0.33 vs 1.43); and combined unique lesions (mean 0.43 and 0.38 vs 1.72), respectively; all $p < 0.001$ versus placebo (Table 1) [41].

■ Safety & tolerability

Lymphocytopenia (graded mostly mild or moderate) was more frequently reported in the cladribine groups (combined cladribine group 26.7 vs 1.8% in placebo), reflecting the mechanism of action of cladribine [41]. Severe neutropenia was reported in three patients receiving cladribine. One of these patients also had severe thrombocytopenia and pancytopenia; the patient turned out to have a reactivation of latent TB and subsequently died. Cladribine probably contributed to this reactivation and TB screening measures were since implemented in ongoing clinical studies to exclude latent or active infection before treatment and retreatment. There was an inverse correlation between the incidence of infection and a patients' lowest lymphocyte count in the combined cladribine group. The median reduction of lymphocyte counts from baseline to the end of the second treatment periods was 43–48%. The nadir (maximum decrease in lymphocyte count) showed a reduction of 45–64% compared with baseline. Herpes zoster infections developed in 20 patients who received cladribine compared with none in the placebo group, but were all dermatomically restricted. The total incidence of serious adverse events was 8.4% in the cladribine 3.5 mg group, 9.0% in the 5.25 mg group and 6.4% in the placebo group. Infections or infestations were reported as serious adverse events in 2.3, 2.9 and 1.6%, respectively. Neoplasms were found only in the cladribine group; a total of four cancers were found: one melanoma, one carcinoma of the

Table 1. The CLARITY Study: clinical and imaging end points after 96 weeks.

Outcome measures		Placebo	Cladribine	
		(n = 437)	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 ARR for cladribine vs placebo (%)	—	57.6 (p < 0.001)	54.5 (p < 0.001)
Relapse-free rate	Patients without relapse; no. (%)	266 (60.9)	345 (79.7) (p < 0.001)	360 (78.9) (p < 0.001)
Time to 3-month sustained change in EDSS	10th percentile of time to event; months	10.8	13.6	13.6
	Hazard ratio for cladribine vs placebo (95% CI)	—	0.67 (0.48–0.93) (p < 0.001)	0.69 (0.49–0.96) (p < 0.001)
Lesion activity on brain MRI				
Gadolinium-enhancing T1-weighted lesions	Mean no. of lesions	0.91	0.12	0.11
	Relative reduction (%)	—	85.7 (p < 0.001)	87.9 (p < 0.001)
Active T2-weighted lesions	Mean no. of lesions	1.43	0.38	0.33
	Relative reduction (%)	—	73.4 (p < 0.001)	76.9 (p < 0.001)
Combined unique lesions	Mean no. of lesions	1.72	0.43	0.38
	Relative reduction (%)	—	74.4 (p < 0.001)	77.9 (p < 0.001)

ARR: Annualized relapse rate; EDSS: Expanded Disability Status Scale.

Adapted from the CLARITY study [39].

pancreas, one carcinoma of the ovary, and one case of cervical carcinoma *in situ* (precancerous) in a patient that had had a positive test for human papillomavirus type 16 at 3 years before diagnosis. The time from the last course of therapy to diagnosis in these four cases was 2, 6, 9 and 7 months, respectively. In addition, a choriocarcinoma was diagnosed 9 months after the study. There were five benign uterine leiomyomas in cladribine-treated patients. The authors commented that the cancers were isolated cases across different organ systems and the small number did not allow for statistical evaluation. There were four deaths during the study and two after discontinuation, equally distributed across the three study groups. In the cladribine 3.5 mg group, one died of myocardial infarction and one of pancreas cancer; in the cladribine 5.25 mg group one died of drowning and one of cardiopulmonary arrest due to reactivation of TB, and in the placebo group one committed suicide and one died of hemorrhagic stroke [41].

■ CLARITY extension study

Clearly there is a need for long-term assessment of efficacy and even more so for surveillance of safety issues. Of the 1326 patients enrolled in the CLARITY study, 802 patients have continued in the 96-week, double-blind, placebo-controlled, parallel-group, multicenter, Phase IIb extension study in which patients originally treated with placebo will be treated with cladribine

tablets at a cumulative dose of 3.5 mg/kg and patients originally treated with cladribine tablets will be randomized to either cladribine tablets 3.5 mg/kg or placebo [45]. This study will mainly provide information on the safety and tolerability of oral cladribine given for another 3 and 4 years and, depending on the adherence of patients to the study, also data on long-term efficacy.

Ongoing & future studies of cladribine in MS

The Oral Cladribine in Early MS (ORACLE) study is a Phase III, 96-week, randomized, double-blind, placebo-controlled, three-arm, multicenter study in patients who have experienced the first demyelinating event within 75 days before screening (clinical isolated syndrome). This trial may be acceptable for patients who wish to start therapy early but cannot overcome injections; however, information regarding concerns on long-term safety, especially regarding possible risk of secondary malignancy must be conferred.

Patients are randomized to receive either cladribine tablets 5.25 or 3.5 mg/kg or matching placebo, as in the CLARITY study. The primary end point is time to conversion to MS according to the revised McDonald criteria [42] and a number of clinical and MRI secondary outcome measures are applied. Any subject who develops clinically definite MS (Poser criteria) [46] during the initial treatment period will enter the maintenance treatment period in which study medication will be discontinued and the

patient will receive open-label IFN- β -1a (Rebif New Formulation) 44 μ g subcutaneously three-times/week for a period of 96 weeks.

Patients who do not develop clinically definite MS in the 96-week initial treatment period will enter a 96-week, long-term follow-up treatment period and receive either open-label cladribine tablets, should they have developed McDonald MS in the initial treatment period, or receive no treatment if they have not developed McDonald MS. At any time during the long-term follow-up period, patients who convert to McDonald MS will receive open-label cladribine. The targeted enrolment is 642 patients.

The Oral Cladribine Added onto IFN- β 1a in Patients with Active Relapsing Disease (ONWARD) study will evaluate the safety and tolerability of cladribine tablets as an add-on therapy to IFN- β [47]. It is a randomized, double-blind, placebo-controlled, 96-week study in patients who, on an established IFN- β therapy, have suffered one or more relapses within the past 48 weeks. Patients will be randomized 1:2 to either placebo or cladribine tablets 3.5 mg/kg. All patients will continue on the IFN- β preparation they received before study entry.

The primary end points are safety events. Incidence of infections, incidence and timing of hematological or hepatic grade 3 and 4 toxicity, and change over time in hematological counts and liver function tests. Exploratory secondary outcomes include relapses and MRI.

After 96 weeks, patients will be asked to continue in the ONWARD follow-up study in which all patients will be treated with cladribine tablets 3.5 mg/kg every 48 weeks for an additional 96 weeks.

The Cladribine Study on Efficacy and Quality of Life (CLASE) study is an open switch study enrolling patients who have had a suboptimal response (defined as at least one relapse within the last 12 months) while receiving IFN- β -1a intramuscularly, IFN- β -1b or glatiramer acetate subcutaneously. All patients will receive cladribine tablets in two courses lasting 4–5 consecutive days separated by a 28-day period. The average dose will be 0.875 mg/kg per course. The study will report relapses, change in EDSS and MRI activity in 48 weeks during which time patients will have been treated with cladribine. Furthermore, a trial in primary progressive MS is expected.

The Post-Approval Safety Study (PASS) is an observational study as a part of a postmarketing risk management plan of cladribine in a ‘real-world’ setting. The study will include approximately 5000 first-time users of oral cladribine for the treatment of MS that will be followed for 8 years allowing a long-term evaluation of possible adverse events, such as severe and selected infections, malignancies and lymphopenia. A supplemental pregnancy registry will be established to follow up female patients who become pregnant during or after cladribine tablet treatment or pregnant partners of male patients.

Cladribine in the hierarchy of disease-modifying drugs for MS

Cladribine has been approved in Russia and for a restricted 2 years of use in Australia. However, it received a negative opinion from the EMA in Europe in September 2010, a decision that has been appealed and awaits the final verdict. In the USA, as of December 2010, the FDA evaluation is ongoing. The reduction of the annualized relapse rate (ARR) in the CLARITY study by 55–58% compared with placebo would seem superior to the approximately 30% reductions seen in the pivotal trials on IFN- β and glatiramer acetate (Figure 3) [48–51]. Nevertheless such comparisons should be assessed by head-to-head studies as the study populations may differ, and it has been noted that relapse rates in general have been lower in recent trials than in the trials from the 1990s [52]. However an evaluation based on both clinical and MRI end points in the CLARITY trial points to a superior effect of cladribine compared with the current first-line DMDs (Figure 3).

Natalizumab, a humanized monoclonal antibody targeting the α -integrins on lymphocytes, administered intravenously once a month for RRMS reduced relapse rates by 68% and the anti-inflammatory effect on MRI lesions was also marked [53]. The drug was well tolerated, but the risk of progressive multifocal leukoencephalopathy (PML) [54], first encountered in the extension of a combination study of natalizumab and IFN- β -1a intramuscularly [55], has limited its use. Labeling information reports that the risk of PML increases with treatment duration and may be higher than one in 1000 treated patients. The exact risk of PML in long-term treatment is unknown. Postmarketing surveillance reports that previous therapy with immunosuppressants (i.e., mitoxantrone and azathioprine) might increase the risk. As of 2 July 2010, 58 cases of PML have been confirmed, of which 12 were fatal [101]. These safety concerns maintain that natalizumab is generally not a first-line therapy, but advisable for patients failing on IFN- β or glatiramer acetate. The efficacy of natalizumab may be superior to that of cladribine in terms of reducing ARR and active lesions on MRI, but cladribine is an immunosuppressant and treatment with cladribine prior to natalizumab might, therefore, increase the risk for PML during subsequent natalizumab therapy. Thus, switching therapy from cladribine to natalizumab is not advisable, whereas the reverse order, placing cladribine as a third-order therapy, might be more favorable than other options, such as mitoxantrone or cyclophosphamide. Mitoxantrone is potent [56], but growing evidence of serious side effects such as infertility [57], cardiotoxicity [58] and acute myeloid leukemia limit its use [59–61].

Fingolimod (FTY720), an oral immunomodulating drug, has been approved in the USA and Russia and is

under review in Europe, therefore, a comparison of these two drugs is of particular interest. Fingolimod is a sphingosine-1-phosphate receptor modulator that prevents the egress of lymphocytes from lymph nodes and thus prevents the extravasation of autoreactive lymphocytes. Fingolimod downregulates the sphingosine-1-phosphate receptors that are found on a variety of target cells and exert different physiological effects on the vascular system, cardiac and endothelial function and tumor angiogenesis. The effect is reversible as cessation of fingolimod treatment causes lymphocytes to reappear in the blood. Similar to cladribine, fingolimod passes through the blood–brain barrier and has potential protective effects on oligodendrocytes [62,63]. Two Phase III studies on oral fingolimod

have recently been published. The Fingolimod Research Evaluating Effects of Daily Oral Therapy in MS (FREEDOMS) study was a randomized double-blind design comparing the efficacy of fingolimod 1.25 or 0.5 mg/day versus placebo [64]. A total of 1272 patients completed this 24-month trial, having a mean EDSS of 2.4 in all three groups at baseline. The ARR was 0.18, 0.16 and 0.40 for fingolimod 0.5, 1.25 mg/day, and placebo, respectively ($p < 0.001$ for either dose vs placebo, representing relative reductions of 54 and 60%, respectively). The key secondary end point was the time to confirmed disability after 3 months (defined as an increase of one point in the EDSS or 0.5 points if the baseline EDSS was 5.5). Both doses significantly reduced the risk of disability progression confirmed at 3 and 6 months. Both doses of fingolimod were superior to placebo with regard to MRI-related measures (number of new or enlarged lesions on T2-weighted images, gadolinium-enhancing lesions and brain volume loss; $p < 0.001$ for all comparisons at 24 months). Similar results were found in Trial Assessing Injectable IFN vs FTY720 Oral in RRMS (TRANSFORMS), a randomized, double-blind, Phase III trial comparing the efficacy and safety of fingolimod 1.25 or 0.5 mg/day with IFN- β -1a (30 μ g) once weekly, given intramuscularly [65]. A total of 1153 patients completed the 12-month trial. The ARR was 0.20 in the 1.25 mg/day fingolimod, 0.16 in the 0.5 mg/day fingolimod compared with 0.33 in the IFN- β -1a-treated group ($p < 0.001$ for both comparisons). Overall, the side effects were mild to moderate, mostly bradycardia, lower respiratory tract infections

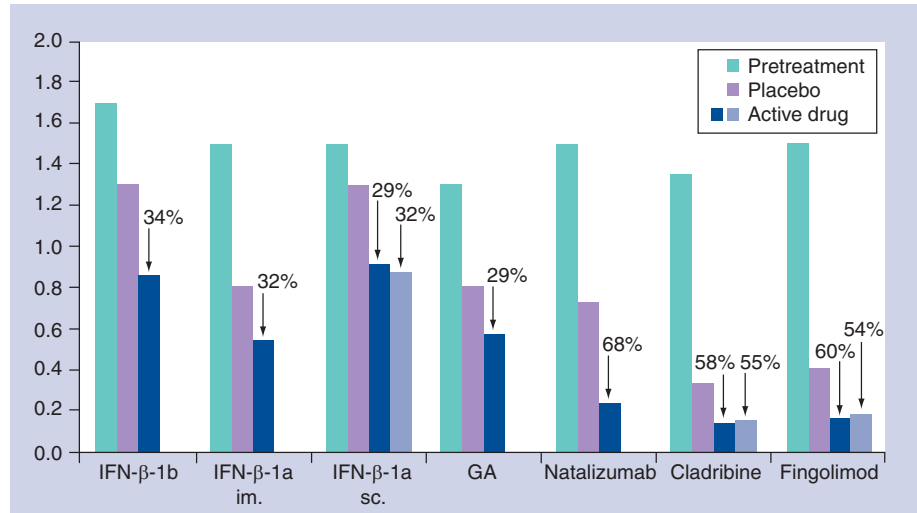


Figure 3. Comparison of the separate pivotal trials regarding reductions on annual relapse rates (y axis) in percentage.

GA: Glatiramer acetate.

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and elevated liver enzymes. Macular edema was found in 13 patients all on the high dose, and all recovered or stabilized after discontinuation of therapy. However, some rare serious adverse events occurred in the fingolimod 1.25 mg group: two patients died, one due to disseminated primary varicella zoster infection and one due to herpes simplex encephalitis. One case of hemorrhaging focal encephalitis has also been reported [66]. One patient died from pneumonia and one from metastatic breast cancer after discontinuation of the drug. Eight skin cancers were reported in the fingolimod group (five basal cell carcinomas and three melanomas) and two in the IFN- β -1a-treated group (one basal and one squamous cell carcinoma) [65,64].

In comparison, the efficacy in terms of ARR between cladribine and fingolimod would seem similar and this is underscored by the marked reduction in MRI lesion activity reported in both studies. However, only fingolimod was tested head-to-head against a first-line DMD (IFN- β -1a). Fingolimod may be discontinued and the side-effects, therefore, theoretically managed. However, three deaths from infections were reported in the fingolimod trials. In both the cladribine- and fingolimod-treated patient groups cancer was reported more frequently than in the placebo groups, but the numbers are too small to provide statistic evaluation. Cladribine and fingolimod, although by different mechanisms, evoke persistent lymphocytopenia and thereby target inflammation, which is considered the key driver of immune-mediated destruction in MS. Both treatments are effective and the choice of therapy might, therefore, primarily

be based on safety and tolerability. Postmarketing observation will disclose the risk of serious infections from treatment with either of the two oral drugs. Another important issue is whether the drugs will be approved as first-line therapies or restrictions in their use will be imposed as is the case for treatment with natalizumab.

Conclusion & future perspective

Multiple sclerosis is a chronic disabling disease, where more efficacious and well-tolerated therapy is needed. First-line DMDs for treatment of relapsing multiple sclerosis are only partially effective and patients may tire of the cumbersome administrations and side effects of self-injection. Many years of parenteral treatment experience with cladribine in MS and cancer has provided a promising efficacy and safety profile. Cladribine is still used as an immunosuppressive agent, but there is growing evidence that it also acts as an immunomodulator of T-cell function. Results from the CLARITY study evaluating the effect of cladribine tablets versus placebo, show a marked reduction of 55–58% in ARR at the end of study at 96 weeks. The formulation and sustained effects of cladribine tablets allow for a very convenient short-course annual dosing regimen. Side effects over a 2-year time span were tolerable, although the long-lasting lymphocyte depletion does require increased surveillance for infections and long-term monitoring is essential to detect unforeseen side effects; for example, possible risk of cancer. Long-term studies, national registries and postmarketing surveillance will be important to detect unexpected adverse effects. Furthermore, the use of cladribine should be carefully considered in women of child-bearing potential and avoided in women planning pregnancy. It is intriguing that cladribine crosses the blood–brain barrier and might, therefore, be effective in progressive forms of MS. Histopathological studies indicate that inflammation may become compartmentalized within the CNS and, therefore, not accessible to first-line DMDs that do not cross the barrier [67].

Given the long-lasting lymphopenia induced with cladribine treatment and lack of safety data beyond

2 years of therapy, we would not recommend cladribine as a first-line treatment for the typical RRMS patients, but would reserve this treatment for patients with very active RRMS or as therapy escalation after breakthrough disease for patients on IFN- β and glatiramer acetate. Provided the extension studies show an acceptable long-term safety profile, cladribine will be an important new therapeutic option as first-line therapy in patients with RRMS. Therefore, the safety observations in ongoing studies are of crucial interest. As the scientific paradigm implies that early and efficacious treatment reducing inflammation in the CNS may be the best option for preventing irreversible disability, the results of the ORACLE MS study in patients with clinically isolated syndrome will be of particular interest.

Notably, several other oral therapies are in Phase III trials and also a number of highly effective monoclonal antibodies are in the late stages of drug development, hence the therapeutic landscape of MS may change rapidly in the coming years.

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Executive summary

- Cladribine is mainly immunosuppressive leading to sustained depletion of CD4⁺ and CD8⁺ T lymphocytes. The frequency of infections is higher than placebo, but tolerable.
- The oral dosing regimen is convenient.
- Efficacy is high. Annual relapse rates are reduced by more than 55–58% compared with placebo; the risk of disability progression and active brain lesions on MRI are reduced.
- The safety profile after 15 years of experience in oncology is promising, but owing to the long-lasting immunosuppression, careful surveillance is needed to detect unforeseen side effects in multiple sclerosis.
- Provided approval, cladribine is an option as third-line therapy in relapsing–remitting multiple sclerosis, after severe breakthrough disease for patients that have been treated with IFN- β , glatiramer acetate and natalizumab.
- Provided an acceptable long-term safety profile, cladribine may be an important new first-line therapeutic option for patients with relapsing–remitting multiple sclerosis.

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