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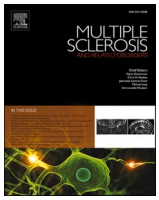

Original article

The real-world efficacy of Cladribine tablets and treatment persistence in people with highly active relapsing multiple sclerosis in Finland – A follow-up study after four years of observation

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ABSTRACT

Background: Cladribine tablets for highly active relapsing multiple sclerosis (MS) have been available in Finland since 2018. The efficacy and safety of cladribine tablets in Finland were reported in 2022. This follow-up study investigated the efficacy, treatment persistence and safety of cladribine tablets after four years.
Methods: Data of subjects who had initiated cladribine tablets for MS in 2018–2020 were acquired from the Finnish MS registry, covering 17 of 21 well-being services counties (ca. 90 % of Finnish patients) in Finland.
Results: Altogether 191 subjects were identified. The mean observation time was 4.6 years (standard deviation [SD] 0.75), and the mean efficacy follow-up was 3.6 years (SD 0.75). Mean annualized relapse rate was 1.0 (SD 0.88) at baseline, and 0.2 (SD 0.33) during the efficacy follow-up. At four years, the estimated probability of first relapse was 0.39 (95 % confidence interval [CI] 0.31–0.45) and the estimated probability of three-month confirmed disability progression (3mCDP) was 0.18 (95 % CI 0.11–0.24). Cladribine tablets were switched to other therapies in 63 subjects (33.0 %), mostly due to inefficacy (52/63, 82.5 %). No differences in the probability of first relapse, 3mCDP or switching therapy were observed between treatment-naive (60/191, 31.4 %) and treatment-experienced (131/191, 68.6 %) subjects. No grade IV lymphopenia and only one case of herpes zoster reactivation (0.5 %) were reported.
Conclusions: Efficacy was comparable across subgroups. Estimated treatment persistence at four years was 70 %. Treatment safety was comparable to previous literature. Adverse events were more frequent in subjects aged 50 years or older at treatment initiation.

1. Introduction

Cladribine is a nucleoside analogue of deoxyadenosine. It belongs to the therapeutic class of selective immunosuppressants. In Finland, cladribine tablets for multiple sclerosis (MS) became available in 2018 and fully reimbursed for highly active MS in 2020. Treatment is administered in two annual courses over two years, and long-term clinical efficacy can last for at least four years. (Giovannoni et al., 2010; Giovannoni et al., 2018) The treatment is considered to elicit its therapeutic effect through a transient selective reduction of B and T lymphocytes followed by immune cell reconstitution. (Ceronie et al., 2018; Giovannoni, 2017; Giovannoni and Mathews, 2022; Sorensen and

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Sellebjerg, 2019)

The efficacy and safety of cladribine tablets in patients with active relapsing MS was first demonstrated in the phase III CLARITY trial. (Giovannoni et al., 2010) Long-term follow-up data from the CLASSIC-MS study demonstrated sustained efficacy, and the extension studies have shown low annualized relapse rates (ARRs) sustained over four years. (Giovannoni et al., 2018, 2023) High efficacy and low treatment burden were also observed in the MAGNIFY-MS and CLARIFY-MS studies. (Brochet et al., 2022; Brochet et al., 2023; de Stefano et al., 2022) Real-world registry data from Italy found that 57 % of patients remained relapse-free for five years after their last dose. (Patti et al., 2020) The cumulative exposure to cladribine tablets is estimated to be over 100 000 patients since the approval by European Medicines Agency (EMA). (Hillert et al., 2024)

Finland is a high-risk region for MS, with approximately 10/100 000 individuals diagnosed yearly. (Pirttisalo et al., 2019) Disease-modifying therapies (DMTs) for MS are mostly prescribed by neurologists working in public healthcare, and treatment decisions are guided by the national Current Care Guidelines. (Multiple Sclerosis: Current Care Guidelines 2024) Reimbursement for prescription medications is provided by The Social Insurance Institution of Finland. For cladribine tablets, the reimbursement criteria are in line with the therapeutic indication evaluated by EMA. Launched in 2014, The Finnish MS registry — a browser-based registry for public healthcare organizations partly integrated into the hospital electronic patient record systems — is used to monitor pwMS in 17 of 21 well-being services counties, including all university hospitals in Finland. (Hämäläinen et al., 2024; Laakso et al., 2019)

Our previous study, published in 2022, used data from the Finnish MS registry to investigate the clinical use of cladribine tablets after a median follow-up time of 19 months. (Rauma et al., 2022) Since then, the need for further information to guide treatment decisions in the long-term has become evident. Uncertainty remains on how to manage disease activation after the initial two years of treatment. Experts have even considered the option of re-dosing cladribine tablets during treatment years 3–4, but in Finland, such re-dosing is not recommended due to concerns of herpes. (Multiple Sclerosis: Current Care Guidelines 2024; Oreja-Guevara et al., 2023) Now that our cohort has reached four years of observation, we set out to investigate the efficacy and treatment persistence of cladribine tablets in Finland.

2. Methods

2.1. Subjects and study data

This non-interventional cohort study was based on data from the Finnish MS registry. In January 2023, the registry included data of 11,349 pwMS. (Hämäläinen et al., 2024) All subjects who had initiated cladribine tablets for MS between 1.1.2018– 31.12.2020 were included. The data cutoff date was 31.5.2024, and the registry data was updated prior to data extraction in all university hospitals.

2.2. Study variables and outcomes

Data for the following variables were extracted: sex (as reported in the Population Information System); date of birth, MS onset and diagnosis; relapses; Expanded Disability Status Scale (EDSS) scores; magnetic resonance imaging (MRI); DMTs; adverse events (AEs); and absolute lymphocyte counts (ALCs). For previous DMTs, all interferons were counted as one. AEs were classified and lymphopenia was stratified according to the Common Terminology Criteria for Adverse Events version 5.0: grade I ($<$1.0–0.8 $\times$ 10^9/L); grade II ($<$0.8–0.5 $\times$ 10^9/L); grade III ($<$0.5–0.2 $\times$ 10^9/L); and grade IV ($<$0.2 $\times$ 10^9/L) lymphopenia. (U.S. Department of Health and Human Services 2017)

Efficacy outcomes included ARRs, first relapse probability, and three-month confirmed disability progression (3mCDP). The probability of switching to other DMTs was used to assess treatment persistence. Safety outcomes included AEs and ALCs. Treatment persistence and safety outcomes were analyzed from cladribine tablet initiation to data cutoff or death ("total observation period"). Efficacy outcomes were analyzed from cladribine tablet initiation to the four-year mark, treatment switch, data cut-off, or death ("efficacy period").

2.3. Group comparisons and additional analyses

Efficacy and treatment persistence were compared between treatment-naive and treatment-experienced subjects. Additional group comparisons used subgroups from our previous study: subjects with 0–1 previous DMTs and those with at least two previous DMTs. (Rauma et al., 2022) Results from the latter analyses were summarized here and are presented in detail in the Supplementary Material.

The clinical characteristics of subjects aged $\geq$50 years when initiating cladribine tablets were investigated. AEs reported in this subgroup are presented in the Supplementary Material. To assess the immediate dosing-related tolerability of cladribine tablets, AEs reported within two weeks after treatment initiation were analyzed.

2.4. Statistics

Data analysis and visualization was performed on pseudo-anonymized data using RStudio (Version 2024.04.1). P-values under 0.05 were considered as significant.

The first dose of cladribine tablets was considered as the index date. Descriptive statistics for demographics and clinical variables included means, standard deviations (SDs), medians, and quartiles (Q1, Q3) for continuous variables, and counts and proportions based on non-missing data for categorical variables. Group comparisons for continuous variables were performed using Student's *t*-test or Wilcoxon rank-sum test depending on data normality. Fisher's exact test was used to compare categorical variables. P-value were adjusted using the Benjamini-Hochberg method for controlling false discovery rate.

Baseline EDSS was defined as the value closest to treatment initiation, ranging from one year before to one month after the index date. Values not within one month of a relapse were prioritized. Each patient's ARR was defined as the number of relapses divided by years of follow-up if follow-up exceeded one year. Baseline ARR was calculated based on the year before cladribine tablet initiation.

Time-to-event endpoints were visualized using cumulative event analyses based on 1−Kaplan–Meier estimates and curves. The log-rank test was utilized to assess differences between overall survival curves. Cox proportional hazard models assessed hazard ratios (HRs) between groups. HRs were reported with 95 % confidence intervals (CIs) and corresponding Wald test p-values. A sensitivity analysis was conducted for time-to-first-relapse after re-baselining six months after cladribine tablet initiation.

Time to 3mCDP was analyzed in subjects with three EDSS measurements available between one year before and six months after the efficacy period endpoint. Disability progression was defined as an EDSS increase of 1.5 points from a baseline EDSS of 0, a 1-point increase from a baseline EDSS of 1–5.5, and a 0.5-point increase after a baseline EDSS of $\geq$6. A three-month confirmation period was used for verification, with confirmation six months after the endpoint of the efficacy period allowed.

2.4. Permissions and ethical considerations

Permission from the Finnish National Institute for Health and Welfare was obtained to allow secondary use of data for this study. A Research Ethics Committee approval or consent was not required according to Finnish legislation, since this was a registry study where subjects were not contacted at any time.

3. Results

3.1. Study cohort

Altogether 191 subjects were identified. The mean total observation time was 4.6 years (SD 0.75), and the mean efficacy period was 3.6 years (SD 0.75). Demographic details, baseline characteristics and comparison between treatment-naive and treatment-experienced subjects are presented in Table 1. Cladribine tablets had been used by 21/191 subjects (11.0 %) who had reached the age of 50 years at treatment initiation (Supplementary Table 1).

Previous DMTs had been used by 131/191 subjects (68.6 %, Fig. 1). The most common last preceding DMTs before cladribine were fingolimod (30/131, 22.9 %), dimethyl fumarate (29/131, 22.1 %) and natalizumab (20/131, 15.3 %). Compared to treatment-naive subjects, those switching from other DMTs were more often males, had a longer median disease duration, and a higher mean age at cladribine tablet initiation (Table 1). They were also characterised by a lower mean ARR, both at diagnosis and at cladribine tablet initiation, as well as a higher median EDSS at cladribine tablet initiation (Table 1).

The demographic details and baseline characteristics of subjects initiating cladribine tablets after 0–1 previous DMTs (101/191 subjects, 52.9 %) and those with two or more previous DMTs (90/191, 47.1 %) are presented in Supplementary Table 2. Subjects with at least two previous DMTs prior to cladribine tablets were older, had a longer mean disease duration, a lower mean baseline ARR, and a higher median baseline EDSS compared to subjects with 0–1 previous DMTs (Supplementary Table 2).

3.2. Efficacy

The four-year mark of the efficacy period was reached by 96/191 subjects (50.3 %). For subjects who did not reach the four-year mark, the efficacy period ended due to a treatment switch (55 subjects, 28.8 %), data cut-off (39 subjects, 20.4 %), or death (one subject, 0.5 %). During the efficacy period, the mean ARR was reduced from 1.0 (SD 0.88) at baseline to 0.2 (SD 0.33).

The estimated probability of first relapse was 0.22 (95 % CI 0.16–0.27) at two years and 0.39 (95 % CI 0.31–0.45) at four years since treatment initiation. Although there were no statistically significant differences in the probability of first relapse between treatment-naive and treatment-experienced subjects, there was a trend towards a higher probability of relapses during the first six months after treatment initiation among subjects switching from other DMTs (Fig. 2A). This trend was no longer seen after re-baselining six months after cladribine tablet initiation (Fig. 2B).

The number of relapses per patient at risk peaked slightly during the first and third years of follow-up (Fig. 2). Altogether 22/191 subjects (11.5 %) experienced a relapse during the first six months after treatment initiation, and almost half of these subjects had switched to cladribine tablets from fingolimod (10/22 subjects, 45.5 %). Out of all subjects who had switched to cladribine tablets from either fingolimod or natalizumab, 10/30 (33.3 %) and 2/20 (10.0 %) experienced a relapse during the first six months after cladribine tablet initiation, respectively. Median washout time from the discontinuation of the last preceding therapy to the initiation of cladribine tablets was 2.9 months (Q1–Q3 1.6–4.3 months) for fingolimod and 3.5 months (Q1–Q3 1.3–5.5 months) for natalizumab.

The estimated probability of 3mCDP was 0.13 (95 % CI 0.07–0.18) at two years and 0.18 (95 % CI 0.11–0.24) at four years since cladribine tablet initiation. There were no statistically significant differences in the risk of 3mCDP between treatment-naive and treatment-experienced subjects (Fig. 3).

When comparing subjects initiating cladribine tablets with either 0–1 previous DMTs or at least two previous DMTs, no statistically significant differences were found in the probability of first relapse (Supplementary Figure 1) or 3mCDP (Supplementary Figure 2). However, a trend towards a higher probability of first relapse during the first six months after treatment initiation was observed among subjects with at least two previous DMTs (Supplementary Figure 1A).

3.3. Treatment persistence

The second-year dose of cladribine tablets was administered to 185/191 subjects in the cohort (96.9 %). After this, additional doses were not administered. During the mean total observation time of 4.6 years,

Table 1
Demographic details and baseline characteristics of the study cohort and comparison between treatment naïve and treatment-experienced subjects. ARR, annualized relapse rate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Q1 and Q3, quartiles; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Variable		All subjects		Treatment naïve subjects		Subjects with previous DMTs		Subjects with data available	*p-value*
		n = 191		*n* = 60		*n* = 131		(n)	
Sex	n (%)							191; 60; 131	*0.02*
Female		162	(84.8)	57	(95.0)	105	(80.2)		
Male		29	(15.2)	3	(5.0)	26	(19.8)		
Age, years	mean (SD)								
at diagnosis		29.6	(8.41)	31.9	(8.61)	28.5	(8.14)	191; 60; 131	*0.07*
at cladribine tablet initiation		35.8	(10.0)	32.9	(9.89)	37.2	(9.82)	191; 60; 131	*0.01*
Time from onset symptom to diagnosis, months	median [Q1, Q3]	9.9	[4.6, 35.0]	7.0	[3.0, 34.3]	11.0	[5.4, 34.9]	177; 59; 118	*0.17*
Disease duration[a], years	median [Q1, Q3]	4.0	[0.3, 11.3]	0.2	[0.1, 0.3]	7.3	[3.5, 13.2]	191; 60; 131	*<0.001*
Year of cladribine tablet initiation	n (%)							191; 60; 131	*0.86*
2018		31	(16.2)	9	(15.0)	22	(16.8)		
2019		73	(38.2)	25	(41.7)	48	(36.6)		
2020		87	(54.5)	26	(43.3)	61	(46.6)		
Course of disease	n (%)							191; 60; 131	
RRMS		188	(98.4)	60	(100.0)	128	(97.7)		
SPMS		3	(1.6)	0	(0.0)	3	(2.3)		
EDSS	median [Q1, Q3]								
at diagnosis		1.5	[1.0, 2.5]	2.0	[1.0, 2.2]	2.0	[1.0, 3.5]	68; 35; 33	*0.72*
at baseline		2.0	[1.0, 3.0]	1.8	[1.0, 2.4]	2.0	[1.0, 3.5]	136; 42; 94	*0.02*
ARR	mean (SD)								
at diagnosis		1.3	(0.80)	1.6	(0.69)	1.2	(0.82)	191; 60; 131	*0.004*
at baseline		1.0	(0.88)	1.7	(0.73)	0.7	(0.78)	191; 60; 131	*<0.001*

[a] Time from diagnosis to cladribine tablet initiation.

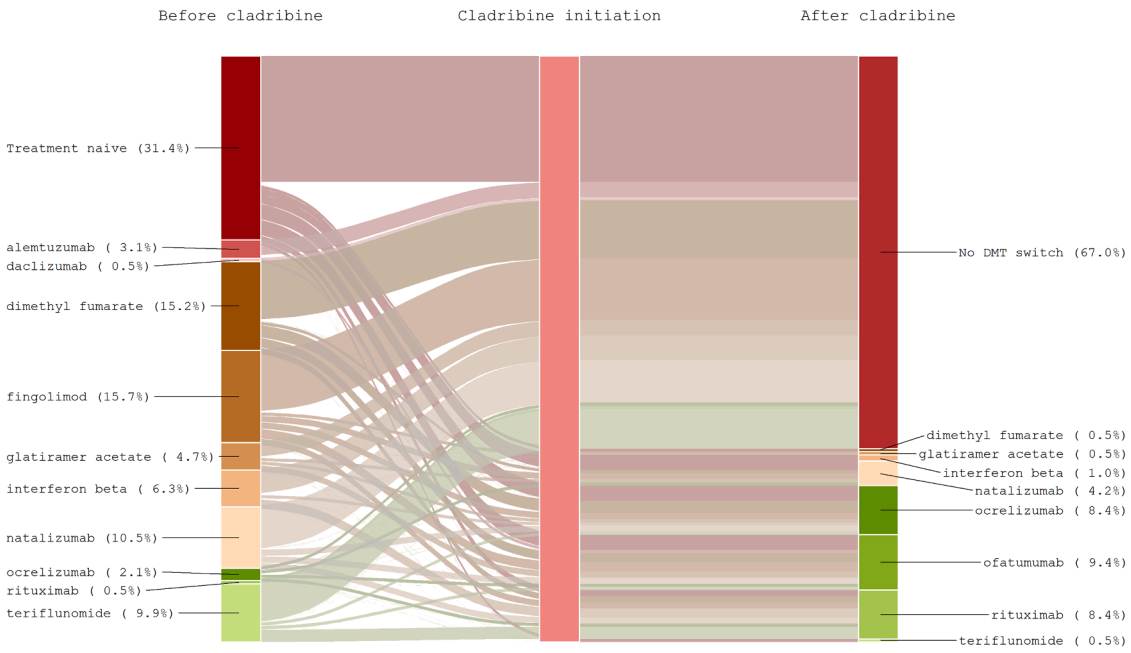


Fig. 1. Treatment sequencing before and after cladribine tablet initiation. DMT, disease-modifying therapy.

cladribine tablets were switched to other DMTs by 63/191 subjects (33.0 %). The most common subsequent therapies after cladribine tablets were anti-CD20 therapies (50/63 subjects, 79.4 %) and natalizumab (8/63, 12.7 %) (Fig. 1).

The reasons for switching therapies included inefficacy (52/63, 82.5 %), adverse events (2/63, 3.2 %), and other/unknown (9/63, 14.3 %). Among subjects switching therapy due to inefficacy, 28/52 subjects (53.8 %) had experienced a relapse within six months prior to the switch. In 11/52 subjects (21.2 %), treatment was switched following MRI activity occurring in the absence of relapses within six months prior to the switch, and in 3/52 subjects (5.8 %), following an increase in EDSS in the absence of any reported inflammatory disease activity within six months before the switch. A total of 10/52 subjects (19.2 %) switched therapy due to inefficacy without recorded cause (no reported relapses, MRI activity or EDSS increase). Mean age at cladribine tablet initiation was slightly lower (31.0 years, SD 8.44) among subjects who switched therapy due to inefficacy when compared to the overall cohort (35.8 years, SD 10.0, descriptive analysis).

The estimated probability of switching therapy was 0.05 (95 % CI 0.02–0.08) at two years and 0.30 (95 % CI 0.23–0.36) at four years since treatment initiation, with no differences between treatment-naive and treatment-experienced subjects (Fig. 4, Supplementary Figure 3). Additionally, there was no difference in the probability of switching therapy between subjects with 0–1 previous DMTs and those with at least two previous DMTs (Supplementary Figure 4). Among subjects aged 50 years or older at the time of cladribine tablet initiation, only 3/21 (14.3 %) switched therapy during their mean total observation time of 4.3 years (SD 0.66). In contrast, 60/170 subjects (35.3 %) younger than 50 years at the time of cladribine tablet initiation switched to other therapies during a mean total observation time of 4.6 years (SD 0.76).

Out of the 22 subjects who had experienced a relapse during the first six months of follow-up, nearly all eventually received their second-year dose of cladribine tablets (20/22 subjects, 90.9 %). However, 13 of these subjects (59.1 %) ended up switching therapy later. Another interesting subgroup included 16/191 subjects (8.4 %) who experienced their first relapse between months 30–36, as shown in Fig. 2. Most of these subjects switched to other DMTs during their observation period (14/16 subjects, 87.5 %).

3.4. Safety

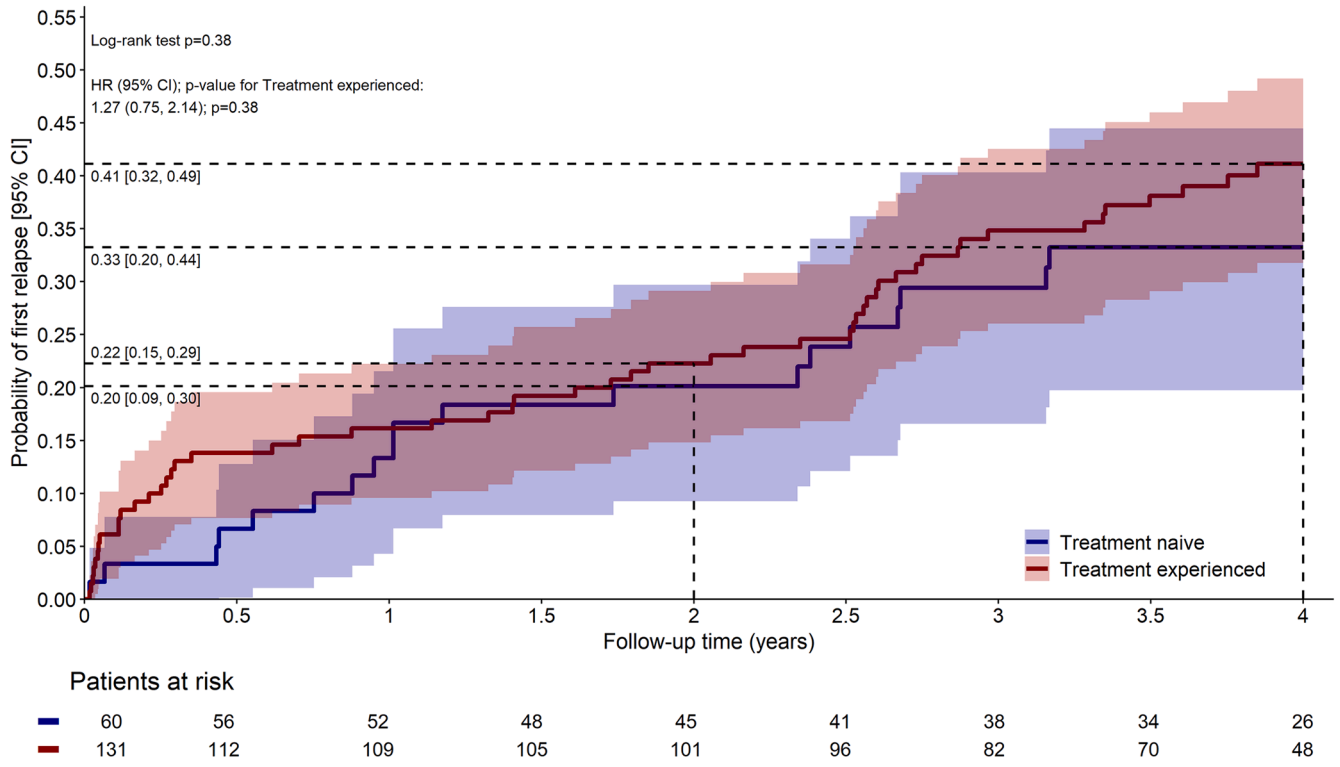
A total of 172 AEs were reported in 33/191 subjects (17.3 %) during the observation period (Table 2). The most prevalent individual AEs were headache (17/191 subjects, 8.9 %), herpes simplex reactivation or infection (7/191 subjects, 3.7 %), and nausea (7/191 subjects, 3.7 %). Two AEs led to a treatment switch: acute pancreatitis and prolonged lymphopenia. As reported in our previous article, one patient died of cardiac arrest. (Rauma et al., 2022)

AEs reported within the first two weeks following the first dose of cladribine tablets were in line with the overall safety profile observed throughout the total observation period (48 events in 16/191 subjects, 8.4 %) (Table 2). The distribution of AEs was similar among subjects aged 50 years or older at initiation (13 events in 8/21 subjects, 38 %) when compared to the total cohort (Supplementary Table 3). However, the incidences of “any AE” and “infections and infestations” in subjects aged 50 years or older at initiation (38.1 % and 19.0 %, respectively) were more than twofold when compared to those in the total cohort (18.8 % and 8.9 %, respectively).

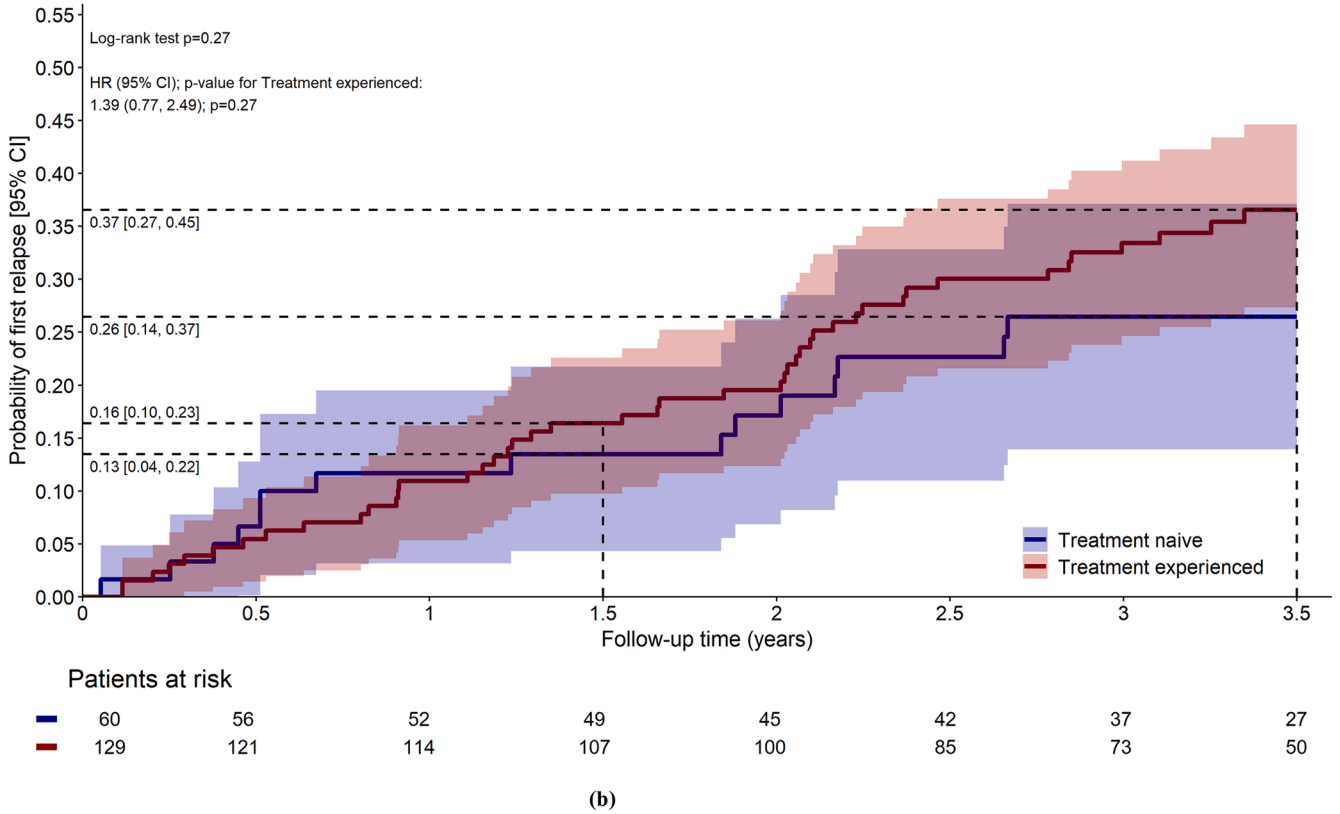
A decrease in mean ALCs was observed after both annual doses, as seen in Fig. 5. Among the 175 subjects with available ALC data, 29 (16.6 %) experienced grade I, 64 (36.6 %) had grade II and 48 (27.4 %) had grade III lymphopenia at some point during the follow-up period. No grade IV lymphopenia was reported. Only two cases of lymphopenia were reported as AEs (Table 2). The mean relative change in lymphocyte counts during follow-up is illustrated in Supplementary Figure 5.

4. Discussion

In our cohort, the estimated probability of a first relapse at four years since cladribine tablet initiation (39 %) was higher than what was reported in the CLARINET-MS study, where 33.8 % of patients from four clinical trials had experienced at least one relapse at 36 months after the last dose. (Patti et al., 2020) Previous real-world studies have not reported the proportion of patients with relapses at exactly four years since treatment initiation. (Lizak et al., 2021; Magalashvili et al., 2022; Rojas et al., 2024; Sorensen et al., 2023; Stępień et al., 2023) A Danish nationwide study with a median follow-up of 35 months after cladribine tablet initiation reported clinical relapses in 25 % of patients. (Sorensen et al., 2023) However, when compared to the subjects in our cohort,



(a)



(b)

Fig. 2. The probability of first relapse, stratified according to previous use of disease-modifying therapies (A) after treatment initiation and (B) after re-baselining six months after treatment initiation. CI, confidence interval; DMT, disease-modifying therapy; HR, hazard ratio.

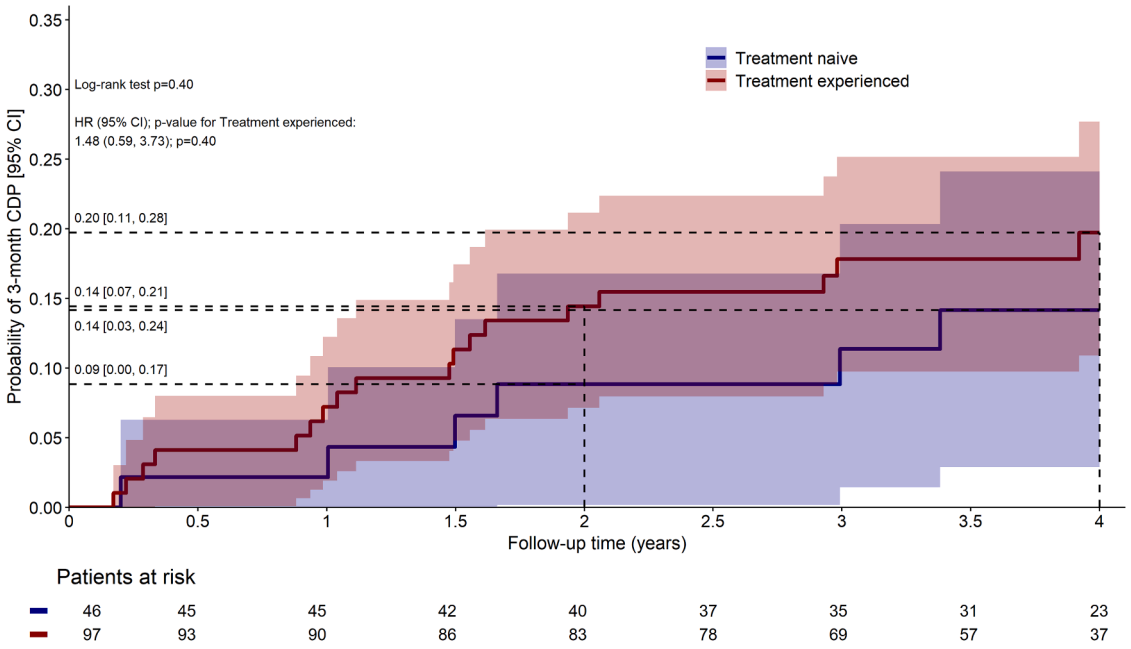


Fig. 3. The probability of three-month confirmed disability progression after treatment initiation, stratified according to previous use of disease-modifying therapies. CDP, confirmed disability progression; CI, confidence interval; DMT, disease-modifying therapy; HR, hazard ratio.

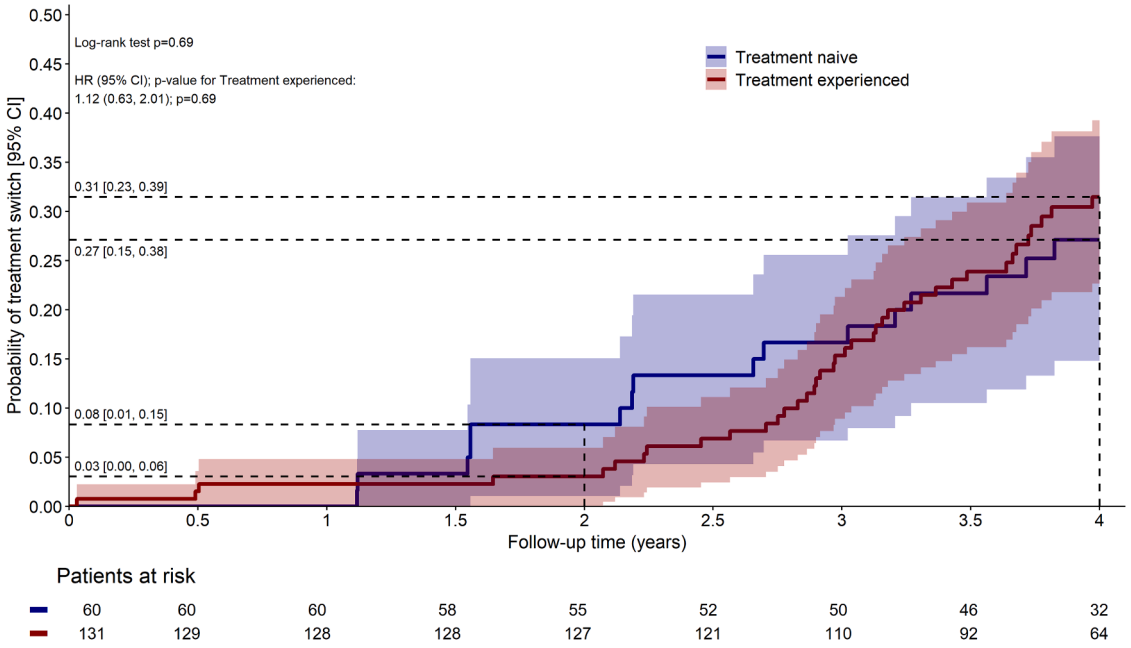


Fig. 4. The probability of switching therapy after treatment initiation stratified according to previous use of disease-modifying therapies. CI, confidence interval; DMT, disease-modifying therapy; HR, hazard ratio.

those in the Danish study were older and had a lower baseline ARR. When compared to the pivotal CLARITY trial, our cohort included a higher proportion of female subjects and more frequent prior use of DMTs. (Giovannoni et al., 2010)

The high probability of a first relapse in our cohort may be related to the level of inflammatory activity among patients eligible for cladribine tablet treatment in Finland. At the time our study subjects received treatment, the reimbursement criteria for cladribine tablets in Finland required either A) the occurrence of two relapses within one year combined with inflammatory activity on MRI, or B) any inflammatory disease activity while receiving another DMT. Our results indicate that when cladribine tablets became available in 2018, they were indeed prescribed as per the official therapeutic indication — to patients with highly active relapsing MS. (European Medicines Agency 2021)

Treatment persistence was lower than expected based on previous real-world studies, although different follow-up durations should be considered. (Kowarik et al., 2024; Manni et al., 2024; Sorensen et al., 2023) Our findings mark a significant development in the understanding of the long-term durability of cladribine tablets, since the estimated treatment persistence was reduced from 95 % at two years to 70 % at four years. In a recent German study, 86 % of patients did not switch treatment within years 1–4. (Kowarik et al., 2024) Even though

Table 2
Adverse events reported during the first two weeks after the first dose of cladribine tablets and during the total observation period.

	Two weeks after first dose		Total observation period	
Subjects with reported event	n	(%)	n	(%)
Any adverse event	17	(8.4)	36	(18.8)
Cardiac disorders			1	(0.5)
Cardiac arrest			1	(0.5)
Gastrointestinal disorders	3	(1.6)	11	(5.8)
Abdominal pain			3	(1.6)
Acute pancreatitis			1	(0.5)
Constipation			1	(0.5)
Diarrhea			3	(1.6)
Dyspepsia	1	(0.5)	1	(0.5)
Nausea	2	(1.0)	7	(3.7)
General disorders and administration site conditions	1	(0.5)	5	(2.6)
Fatigue	1	(0.5)	3	(1.6)
Malaise			2	(1.0)
Infections and infestations	5	(2.6)	16	(8.4)
Respiratory infections				
COVID-19 infection with fever			1	(0.5)
Upper respiratory infection	1	(0.5)	3	(1.6)
Unspecified respiratory infection	1	(0.5)	1	(0.5)
Skin infections				
Pustular or papulopustular rash			3	(1.6)
Unspecified skin infection			3	(1.6)
Urinary tract infection			1	(0.5)
Vaginal infection			1	(0.5)
Other				
Abscess	1	(0.5)	1	(0.5)
Herpes simplex[a]	2	(1.0)	7	(3.7)
Herpes zoster	1	(0.5)	1	(0.5)
Mastitis			1	(0.5)
Unspecified infection			1	(0.5)
Investigations			3	(1.6)
Lymphocyte count decreased[b]			2	(1.0)
Weight loss			1	(0.5)
Musculoskeletal and connective tissue disorders	1	(0.5)	2	(1.0)
Back pain	1	(0.5)	2	(1.0)
Nervous system disorders	9	(4.7)	18	(9.4)
Dizziness			1	(0.5)
Dysesthesia	1	(0.5)	1	(0.5)
Headache	9	(4.7)	17	(8.9)
Psychiatric disorders			1	(0.5)
Insomnia			1	(0.5)
Skin and subcutaneous tissue disorders	2	(1.0)	6	(3.1)
Alopecia	1	(0.5)	3	(1.6)
Pruritus			2	(1.0)
Rash				
Acneiform rash	1	(0.5)	1	(0.5)
Unspecified rash			1	(0.5)

[a] Reactivation or primary infection.
[b] Only clinically significant lymphopenias were most likely reported as adverse events.

inefficacy was the most common reason for switching treatment in our cohort, only about half of the subjects switching due to inefficacy had a reported clinical relapse prior to the switch, whereas 21.2 % were reported to have MRI activity without relapses. Because coverage of MRI data in the Finnish MS registry may be lower than that of clinical data, we suspect that the actual number of switches based on radiological activity could be higher.

Despite the rather linear accumulation of relapses since treatment initiation (Fig. 2), a similar increase in the probability of switching treatment was not seen until the third year of follow-up (Fig. 4). This observation may support the hypothesis that clinicians anticipated that the full efficacy of cladribine tablets would be achieved after a longer follow-up, and consequently, chose not to escalate treatment in the occurrence of relapses during years 1–2. We suggest that early monitoring — starting with a re-baseline MRI at six months since treatment initiation — is likely useful in identifying patients with ongoing inflammatory activity. The fact that anti-CD20 therapies were most frequently chosen as the next subsequent therapy reflects our current therapeutic options and treatment guidelines as well as the scarcity of data regarding the re-dosing of cladribine tablets. (Multiple Sclerosis: Current Care Guidelines 2024)

The estimated probability of 3mCDP at four years was in line with the previously reported CLARITY EXT post hoc analysis. (G Giovannoni et al., 2021) We did not observe any statistically significant differences in the probability of first relapse or 3mCDP between treatment-naive and treatment-experienced subjects. This contradicts some earlier studies suggesting a potentially higher efficacy among treatment-naive individuals. (Arena et al., 2024; Zanetta et al., 2023) In line with our previous study, we demonstrated that clinical disease reactivation was common among subjects switching from fingolimod, whereas those switching from natalizumab were relatively stable. (Rauma et al., 2022) However, it is difficult to draw conclusions about whether cladribine tablets could prevent post-natalizumab disease reactivation since the washout times observed in our cohort were long. Previous studies have demonstrated that switching from natalizumab to cladribine tablets is associated with an increased risk for relapses, but a phase IV trial (CLADRINA) is currently underway to further test this strategy. (Pfeuffer et al., 2022; Sguigna et al., 2024; Zhong et al., 2023)

Cladribine tablets have been considered well-tolerated based on previous studies. (Cook et al., 2019) In our cohort, AEs were reported in 17.3 % of the study subjects, and only two subjects discontinued due to AEs. One single case of pancreatitis (0.5 %) with no obvious cause was identified. The very low incidence of herpes zoster reactivation in our cohort is noteworthy, especially since a relative rarity of this AE when compared to the CLARITY extension trial was also reported in a Danish study. (Giovannoni et al., 2018; Sorensen et al., 2023), We hypothesize that the absence of grade IV lymphopenia in our cohort together with possible confounding variables related to the study population may be linked to the low incidence of herpes zoster.

Recently, cladribine tablets have been suggested as an alternative to continuously administered therapies in aging individuals with MS. (de Seze et al., 2024) Although data on the use of cladribine tablets in this subgroup is sparse, no special safety concerns have been described. (Disanto et al., 2022; Giovannoni et al., 2021) In our study, AEs (and especially infections and infestations) were numerically more frequent among subjects aged 50 years or older at treatment initiation, but the total number of reported AEs was still low. Larger pharmacovigilance studies in this age group would be valuable to further assess the safety of cladribine tablets in individuals aged 50 years or older.

Our study had the benefit of analyzing subjects with highly active relapsing MS in a nearly nationwide population-based cohort. Data was affirmed using unified criteria by the researchers in all university hospitals, which increased the validity of our data. Efficacy outcomes should be interpreted with caution due to the significant proportion of subjects who switched therapy, since the approach used to define “efficacy period” in our study could introduce survivor bias. Our efficacy metrics may represent a selected group of subjects who were able to continue therapy, and therefore, may overestimate the efficacy of cladribine tablets on a population level. Limitations include the potential of missing data in central hospitals. MRI data were not systematically recorded, so we were unable to analyze MRI activity or ‘no evidence of disease activity’ (NEDA) status in detail. Follow-up practices likely varied between hospitals, and reasons for treatment persistence were partly unreached by this study. Our results cannot be used to compare treatment strategies after disease activation, since efficacy outcomes were not analyzed beyond treatment switches. Also, questions regarding the re-dosing of cladribine remain unanswered, since according to our data, additional courses of cladribine tablets have not been administered in Finland.

In conclusion, the probability of first relapse was high in this nearly

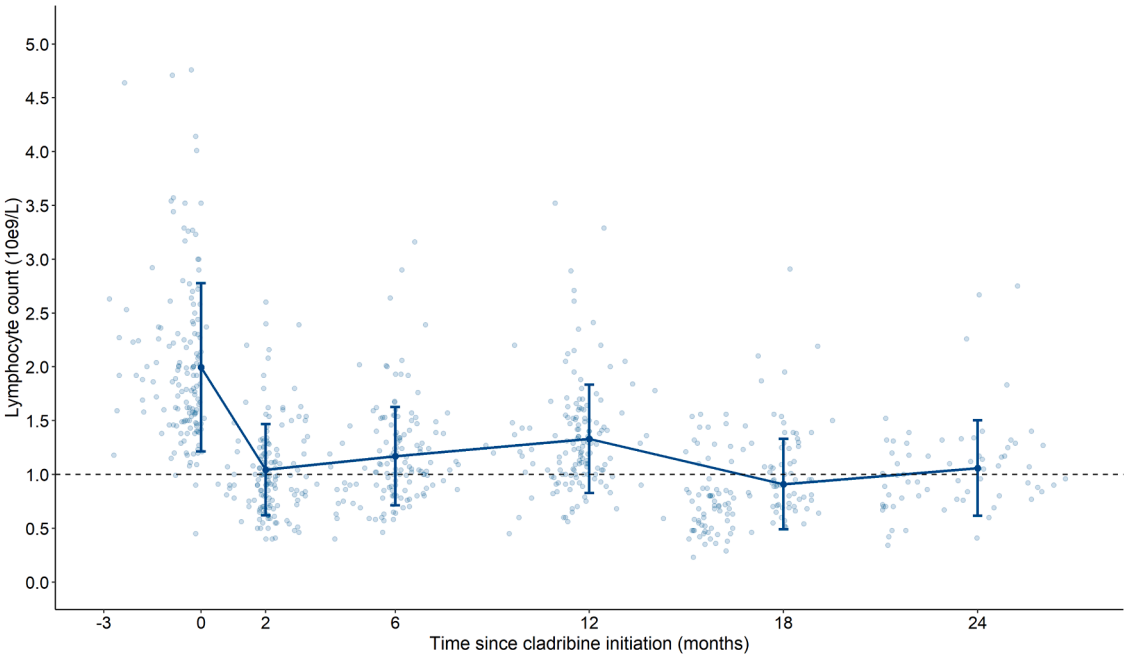


Fig. 5. Lymphocyte counts (10^9/L) before and after the initiation of cladribine tablets. Means (circles) and standard deviations (bars) of lymphocyte counts are illustrated at time points of special interest.

nationwide cohort of Finnish subjects treated with cladribine tablets for highly active relapsing MS. Estimated treatment persistence at four years was 70 %. No differences were observed in the probability of first relapse or 3mCDP between subjects who were treatment naive and those switching from other DMTs. The incidence of infections was low, with only incidental cases of herpes simplex and a single case of herpes zoster. The safety profile of cladribine tablets among subjects aged 50 years or older at initiation was in line with the overall cohort, but AEs were numerically more frequent in this subgroup. This kind of registry-based real-world evidence is extremely valuable in assessing the efficacy and safety of DMTs for MS in diverse populations. Based on our observations, we suggest that careful patient selection, short washout times, and early monitoring of treatment response are important when initiating cladribine tablets.

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Data availability statement

The raw data required to reproduce our findings cannot be shared due to legal and ethical reasons. However, aggregate data to support our findings are available from the authors upon a reasonable request.

CRediT authorship contribution statement

Ilkka Rauma: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **Matias Viitala:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Merja Soilu-Hänninen:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Sari Atula:** Writing – review & editing, Methodology, Investigation. **Sini Laakso:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Hanna Kuusisto:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Marja Niiranen:** Writing – review & editing, Methodology, Investigation. **Mervi Ryytty:** Writing – review & editing, Methodology, Investigation. **Visa Manni:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2025.106724.

References

Arena, S., Chisari, C.G., Toscano, S., et al., 2024. Real-world effectiveness of Cladribine for patients with multiple sclerosis: a Sicilian multicentric experience (Rewind Study). Curr. Neuropharmacol. 22 (7), 1271–1283. https://doi.org/10.2174/1570159X21666230322140711.

Brochet, B., Hupperts, R., Langdon, D., et al., 2022. Treatment satisfaction, safety, and tolerability of cladribine tablets in patients with highly active relapsing multiple sclerosis: CLARIFY-MS study 6-month interim analysis. Mult. Scler. Relat. Disord. 57, 103385. https://doi.org/10.1016/j.msard.2021.103385.

Brochet, B., Solari, A., Lechner-Scott, J., et al., 2023. Improvements in quality of life over 2 years with cladribine tablets in people with relapsing multiple sclerosis: the CLARIFY-MS study. Mult. Scler. 29 (14), 1808–1818. https://doi.org/10.1177/13524585231205962.

Ceronie, B., Jacobs, B.M., Baker, D., et al., 2018. Cladribine treatment of multiple sclerosis is associated with depletion of memory B cells. J. Neurol. 265 (5), 1199–1209. https://doi.org/10.1007/s00415-018-8830-y.

Cook, S., Leist, T., Comi, G., et al., 2019. Safety of cladribine tablets in the treatment of patients with multiple sclerosis: an integrated analysis. Mult. Scler. Relat. Disord. 29, 157–167. https://doi.org/10.1016/j.msard.2018.11.021.

de Seze, J., Dive, D., Ayrignac, X., et al., 2024. Narrative review on the use of cladribine tablets as exit therapy for stable elderly patients with Multiple sclerosis. Neurol. Ther. 13 (3), 519–533. https://doi.org/10.1007/s40120-024-00603-y.

de Stefano, N., Barkhof, F., Montalban, X., et al., 2022. Early reduction of MRI activity during 6 months of treatment with cladribine tablets for highly active relapsing multiple sclerosis: MAGNIFY-MS [published correction appears in Neurol Neuroimmunol Neuroinflamm. 2022 Oct 20;9(6):e200061. doi: 10.1212/NXI.0000000000200061.]. Neurol. Neuroimmunol. Neuroinflamm. 9 (4), e1187. https://doi.org/10.1212/NXI.0000000000001187. Published 2022 Jun 14.

Disanto, G., Moccia, M., Sacco, R., et al., 2022. Monitoring of safety and effectiveness of cladribine in multiple sclerosis patients over 50 years. Mult. Scler. Relat. Disord. 58, 103490. https://doi.org/10.1016/j.msard.2022.103490.

European Medicines Agency, 2021. MAVENCLAD EU summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/mavenclad-epar-product-information_en.pdf (accessed 3 Feb 2025).

Giovannoni, G., Boyko, A., Correale, J., et al., 2023. Long-term follow-up of patients with relapsing multiple sclerosis from the CLARITY/CLARITY Extension cohort of CLASSIC-MS: an ambispective study. Mult. Scler. 29 (6), 719–730. https://doi.org/10.1177/13524585231161494.

Giovannoni, G., Comi, G., Cook, S., et al., 2010. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N. Engl. J. Med. 362 (5), 416–426. https://doi.org/10.1056/NEJMoa0902533.

Giovannoni, G., Comi, G., Rammohan, K., et al., 2021a. Long-term disease stability assessed by the expanded disability status scale in patients treated with cladribine tablets 3.5 mg/kg for relapsing multiple sclerosis: an exploratory post hoc analysis of the CLARITY and CLARITY extension studies. Adv. Ther. 38 (9), 4975–4985. https://doi.org/10.1007/s12325-021-01865-w.

Giovannoni, G., Coyle, P.K., Vermersch, P., et al., 2021b. Integrated lymphopenia analysis in younger and older patients with multiple sclerosis treated with cladribine tablets. Front. Immunol. 12, 763433. https://doi.org/10.3389/fimmu.2021.763433. Published 2021 Dec 24.

Giovannoni, G., Mathews, J., 2022. Cladribine tablets for relapsing-remitting multiple sclerosis: a clinician's review. Neurol. Ther. 11 (2), 571–595. https://doi.org/10.1007/s40120-022-00339-7.

Giovannoni, G., Soelberg Sorensen, P., Cook, S., et al., 2018. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: results from the randomized extension trial of the CLARITY study. Mult. Scler. 24 (12), 1594–1604. https://doi.org/10.1177/1352458517727603.

Giovannoni, G., 2017. Cladribine to treat relapsing forms of Multiple sclerosis. Neurotherapeutics. 14 (4), 874–887. https://doi.org/10.1007/s13311-017-0573-4.

Hämäläinen, P., Viitala, M., Kuusisto, H., Ruutiainen, J., Soilu-Hänninen, M., 2024. MyMS: an interface for patient-reported outcomes for Finnish individuals with multiple sclerosis. Int. J. MS. Care 26 (Q4), 273–280. https://doi.org/10.7224/1537-2073.2023-082. Published 2024 Oct 7.

Hillert, J., Butzkueven, H., Magyari, M., et al., 2024. Harmonized data quality indicators maintain data quality in long-term safety studies using multiple sclerosis registries/data sources: experience from the CLARION study. Clin. Epidemiol. 16, 717–732. https://doi.org/10.2147/CLEP.S480525. Published 2024 Oct 17.

Kowarik, M.C., Ernst, M., Woitschach, L., et al., 2024. Real-world therapy management of patients with multiple sclerosis receiving cladribine tablets beyond year 4 - results from a German cladribine cohort. Mult. Scler. Relat. Disord. 88, 105704. https://doi.org/10.1016/j.msard.2024.105704.

Laakso, S.M., Viitala, M., Kuusisto, H., et al., 2019. Multiple sclerosis in Finland 2018-data from the national register. Acta Neurol. Scand. 140 (5), 303–311. https://doi.org/10.1111/ane.13145.

Lizak, N., Hodgkinson, S., Butler, E., et al., 2021. Real-world effectiveness of cladribine for Australian patients with multiple sclerosis: an MSBase registry substudy. Mult. Scler. 27 (3), 465–474. https://doi.org/10.1177/1352458520921087.

Magalashvili, D., Mandel, M., Dreyer-Alster, S., et al., 2022. Cladribine treatment for highly active multiple sclerosis: real-world clinical outcomes for years 3 and 4. J. Neuroimmunol. 372, 577966. https://doi.org/10.1016/j.jneuroim.2022.577966.

Manni, A., Oggiano, F., Palazzo, C., et al., 2024. Clinical and biological predictors of Cladribine effectiveness in Multiple Sclerosis: a real-world, single centre study considering a two-year interval from year-2 dosing. J. Neurol. Sci. 462, 123070. https://doi.org/10.1016/j.jns.2024.123070.

Multiple Sclerosis: Current Care Guidelines, 2024. Working group appointed by the finnish medical society duodecim and the finnish neurological society. https://www.kaypahoito.fi/hoi36070 (In Finnish) (accessed 5 Feb 2025).

Oreja-Guevara, C., Brownlee, W., Celius, E.G., et al., 2023. Expert opinion on the long-term use of cladribine tablets for multiple sclerosis: systematic literature review of real-world evidence. Mult. Scler. Relat. Disord. 69, 104459. https://doi.org/10.1016/j.msard.2022.104459.

Patti, F., Visconti, A., Capacchione, A., Roy, S., Trojano, M., CLARINET-MS Study Group, 2020. Long-term effectiveness in patients previously treated with cladribine tablets: a real-world analysis of the Italian multiple sclerosis registry (CLARINET-MS). Ther. Adv. Neurol. Disord. 13, 1756286420922685. https://doi.org/10.1177/1756286420922685. Published 2020 Jun 10.

Pfeuffer, S., Rolfes, L., Hackert, J., et al., 2022. Effectiveness and safety of cladribine in MS: real-world experience from two tertiary centres. Mult. Scler. 28 (2), 257–268. https://doi.org/10.1177/13524585211012227.

Pirttisalo, A.L., Soilu-Hänninen, M., Sipilä, J.O.T., 2019. Multiple sclerosis epidemiology in Finland: regional differences and high incidence. Acta Neurol. Scand. 139 (4), 353–359. https://doi.org/10.1111/ane.13057.

Rauma, I., Viitala, M., Kuusisto, H., et al., 2022. Finnish multiple sclerosis patients treated with cladribine tablets: a nationwide registry study. Mult. Scler. Relat. Disord. 61, 103755. https://doi.org/10.1016/j.msard.2022.103755.

Rojas, J.I., Alonso, R., Luetic, G., et al., 2024. Real-world effectiveness and safety of cladribine in Multiple sclerosis: longitudinal data from the nationwide registry in Argentina. Clin. Neuropharmacol. 47 (4), 120–127. https://doi.org/10.1097/WNF.0000000000000598.

Sguigna, P.V., Hussain, R.Z., Okai, A., et al., 2024. Cladribine tablets after treatment with natalizumab (CLADRINA) - rationale and design. Ther. Adv. Neurol. Disord. 17, 17562864241233858. https://doi.org/10.1177/17562864241233858. Published 2024 Apr 4.

Sorensen, P.S., Pontieri, L., Joensen, H., et al., 2023. Real-world experience of cladribine treatment in relapsing-remitting multiple sclerosis: a Danish nationwide study. Mult. Scler. Relat. Disord. 70, 104491. https://doi.org/10.1016/j.msard.2022.104491.

Sorensen, P.S., Sellebjerg, F., 2019. Pulsed immune reconstitution therapy in multiple sclerosis. Ther. Adv. Neurol. Disord. 12, 1756286419836913. https://doi.org/10.1177/1756286419836913. Published 2019 Mar 28.

Stępień, A., Pogoda-Wesołowska, A., Tokarz-Kupczyk, E., et al., 2023. Cladribine tablets for highly active relapsing-remitting multiple sclerosis in Poland: a real-world, multicentre, retrospective, cohort study during the COVID-19 pandemic. Neurol. Neurochir. Pol. 57 (4), 371–378. https://doi.org/10.5603/PJNNS.a2023.0050.

U.S. Department of Health and Human Services, 2017. National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

Zanetta, C., Rocca, M.A., Meani, A., et al., 2023. Effectiveness and safety profile of cladribine in an Italian real-life cohort of relapsing-remitting multiple sclerosis patients: a monocentric longitudinal observational study [published correction appears in J Neurol. 2023 Jul;270(7):3565-3566. doi: 10.1007/s00415-023-11772-5.]. J. Neurol. 270 (7), 3553–3564. https://doi.org/10.1007/s00415-023-11700-7.

Zhong, M., van der Walt, A., Monif, M., et al., 2023. Prediction of relapse activity when switching to cladribine for multiple sclerosis. Mult. Scler. 29 (1), 119–129. https://doi.org/10.1177/13524585221111677.