Finnish multiple sclerosis patients treated with cladribine tablets : a nationwide registry study

Rauma, Ilkka

2022-05

Rauma , I , Viitala , M , Kuusisto , H , Atula , S , Sipilä , J O T , Ryytty , M , Soilu-Hanninen , M & Järvinen , E 2022 , ' Finnish multiple sclerosis patients treated with cladribine tablets : a nationwide registry study ' , Multiple sclerosis and related disorders , vol. 61 , 103755 . https://doi.org/10.1016/j.msar

http://hdl.handle.net/10138/351497
https://doi.org/10.1016/j.msard.2022.103755

Multiple Sclerosis and Related Disorders 61 (2022) 103755

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Finnish multiple sclerosis patients treated with cladribine tablets: a nationwide registry study

Ilkka Rauma [a,b,§,*], Matias Viitala [c], Hanna Kuusisto [b,d,$], Sari Atula [e,f], Jussi O T Sipilä [g,h,£], Mervi Ryytty [i,j], Merja Soilu-Hänninen [h,k,#], Elina Järvinen [l]

[a] Tampere University, Faculty of Medicine and Health Technology, Tampere, Finland
[b] Tampere University Hospital, Department of Neurology, Tampere, Finland
[c] StellarQ Ltd., Turku, Finland
[d] University of Eastern Finland, Department of Health and Social Management, Kuopio, Finland
[e] Helsinki University Hospital, Neurocenter, Helsinki, Finland
[f] University of Helsinki, Department of Neurosciences, Helsinki, Finland
[g] Siun Sote, North Karelia Central Hospital, Department of Neurology, Joensuu
[h] Clinical Neurosciences, University of Turku, Turku, Finland
[i] University of Oulu, Research Unit of Clinical Neuroscience, Neurology, Oulu, Finland
[j] Oulu University Hospital, Medical Research Center, Oulu, Finland
[k] Turku University Hospital, Neurocenter, Turku, Finland
[l] Merck Oy, Espoo, Finland, an affiliate of Merck KGaA

ARTICLE INFO

Keywords:
cladribine tablets
Finland
multiple sclerosis
real-world data
registries
treatment outcome

ABSTRACT

Background: Cladribine tablets for adult patients with highly active relapsing multiple sclerosis (MS) have been available in Finland since 2018. Real-world data from different genetic and geographical backgrounds are needed to complement data from clinical trials.

Methods: We investigated the use of cladribine tablets in Finland in a non-interventional cohort study, based on real-world data from the nationwide Finnish MS registry. All eligible patients who had initiated treatment with cladribine tablets in 2018-2020 were included. Descriptive analyses for outcomes were conducted using summary statistics. Time-dependent endpoints were analyzed using cumulated events analysis based on 1-Kaplan–Meier estimates and curves. Subgroups were analyzed separately according to the number of previous disease-modifying therapies (DMTs) and the most common last preceding therapies.

Results: Data of 179 patients were analyzed. Median follow-up time was 19.0 months (interquartile range [IQR] 12.0-26.2). Of the 134 patients who were followed for at least 12 months, 112 patients (83.6%) remained relapse-free during follow-up. Mean annualized relapse rate (ARR) was 1.0 (standard deviation [SD] 0.89) at baseline, and 0.1 (SD 0.30) at follow-up. Patients with two or more previous DMTs had shorter time to first relapse (median 2.5 months, IQR 0.6-9.3) when compared to patients with 0-1 previous DMTs (median 11.4 months, IQR 8.7-13.1) (p=0.013). After excluding patients switching from fingolimod (n=33), a statistically significant difference in time to first relapse was no longer observed between the two groups (p=0.252). Adverse events (AEs) were reported in 30 patients (16.8%). The most frequent AE was headache (n=14, 7.8%). One patient (0.6%) died of cardiac arrest. Discontinuation of cladribine tablets was reported in nine patients (5.0%).

Abbreviations: ALC, absolute lymphocyte count; AE, adverse event; ARR, annualized relapse rate; CD, cluster of differentiation; CTCAE, Common Terminology Criteria for Adverse Events; DMF, dimethyl fumarate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IQR, interquartile range; JC virus, John Cunningham virus; mo, months; MRI, magnetic resonance imaging; MS, multiple sclerosis; SF, standard deviation.

* Corresponding author.
E-mail address: ilkka.rauma@tuni.fi (I. Rauma).
§ 0000-0002-3275-9631
$ 0000-0002-3697-4961
£ 0000-0003-0183-9054
0000-0001-6930-0229

https://doi.org/10.1016/j.msard.2022.103755
Received 26 January 2022; Received in revised form 7 March 2022; Accepted 18 March 2022
Available online 19 March 2022

Conclusion: The mean ARR observed in this cohort was similar to what has been reported in clinical trials. Approximately half of the patients had used two or more previous DMTs before cladribine tablets. These patients had a shorter time to first relapse when compared to patients with 0-1 previous DMTs, mostly driven by early relapses in patients switching from fingolimod.

1. Introduction

Cladribine tablets for adult patients with highly active relapsing multiple sclerosis (MS) have been available in Finland since 2018 and fully reimbursed since 2020. Cladribine tablets are administered in two annual courses over two years (MAVENCLAD EU SmPC, 2021). Long-term clinical efficacy is expected to be acquired after full dosing, and can last for at least four years (Giovannoni et al., 2018, 2010). Treatment with cladribine leads to a transient reduction of B and T lymphocytes (Comi et al., 2019). There is a greater reduction of CD19+ B cells than CD4+ and CD8+ T cells (Comi et al., 2019). The subsequent lymphocyte kinetics, recovery of lymphocyte counts, and the reconstitution of immune function have been thought to explain the long-term therapeutic effect of cladribine (Stuve et al., 2019). Preferential reduction of memory B cells has been proposed to be the main driver of the therapeutic effect of cladribine (Ceronie et al., 2018).

Finland is a high-risk region for MS with an age-standardized prevalence ranging from 149/100 000 in Pirkanmaa to 276/100 000 in South Ostrobothnia during 2010-2016 (Pirttisalo et al., 2020). The national Finnish MS registry is used at both university and central hospitals to record attributes of MS patients during clinical practice (Laakso et al., 2019). The collected data can also be used for nationwide real-world studies.

Real-world data on cladribine tablets is still limited to a few cohorts (Bose et al., 2021; Lizak et al., 2021; Möhn et al., 2019; Patti et al., 2020; Pfeuffer et al., 2021; Rolfes et al., 2021). In the pivotal phase III CLARITY trial, patients who had failed two or more previous DMTs were excluded (Giovannoni et al., 2010). As a result, there is a need for real-world studies investigating the use of cladribine tablets especially in patients who have received at least two previous DMTs before cladribine treatment. The present study offers new insights into this subgroup of patients.

Here, we report the demographic details and clinical outcomes of patients treated with cladribine tablets from our non-interventional nationwide real-world cohort study in Finland. We set out to investigate treatment sequencing and the impact of previous disease-modifying therapies (DMTs) on clinical outcomes in patients treated with cladribine tablets.

2. Material and methods

2.1. Study design and outcomes

All patients in the Finnish MS registry who had initiated treatment with cladribine tablets for MS from January 1, 2018, to December 31, 2020, in the clinical setting were included. Data entries to the registry had been made either manually by health care professionals or by integration from hospital administrative data (Laakso et al., 2019). Demographic and clinical data were extracted on May 31, 2021. In the five hospital districts represented by authors IR, HK, SA, JOTS, MR, and MS-H, the registry data had been updated immediately prior to data extraction to minimize missing data. Magnetic resonance imaging (MRI) data were not included, as the national coverage of MRI data in the registry was insufficient for this study. When calculating the number of previous DMTs, all interferon treatments were grouped as one therapy. Discontinuation of cladribine tablets was defined as any of the following: an end date had been recorded (if, for example, the second-year dosing had been withheld); a new DMT had been initiated; or patient died during follow-up. Follow-up time was calculated from the first dose to either death, treatment switch minus one day (if a subsequent DMT had been initiated), or data extraction (if the patient was alive and no other DMT had been initiated). Efficacy outcomes included number of relapses, annualized relapse rate (ARR), time to first relapse, and Expanded Disability Status Scale (EDSS). Safety outcomes included adverse events (AEs) and absolute lymphocyte counts (ALCs). Lymphopenia was stratified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (U.S. Department of Health and Human Services, National Institutes of Health, 2017): 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.

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

2.2. Statistical analysis

Data analysis and visualization was performed on pseudo-anonymized data using RStudio (Version 1.4.1103). Descriptive analyses were conducted using summary statistics. Numerical variables were expressed as means with standard deviations (SDs) or medians with interquartile ranges (IQRs). Categorical variables were expressed as frequencies and proportions based on non-missing data. Group comparisons for continuous variables were performed using the Wilcoxon rank-sum test or Student's t-test depending on the normality of the groups, and for the categorical variables using Fisher's exact test. For controlling and checking the False Discovery Rate, Benjamini–Hochberg procedure was used as a correction for multiple comparisons in demographic and clinical variables. Time-dependent endpoints were analyzed using cumulated events analysis based on 1-Kaplan–Meier estimates and curves. Log-rank test was utilized to assess differences between overall event probabilities.

Baseline EDSS was defined as the last recorded EDSS within one year before treatment initiation, and baseline ARR was defined as the number of relapses during that year. Two subgroup analyses were performed. The first comparison was between patients with two or more previous DMTs and patients with 0-1 previous DMTs prior to cladribine tablets. Group comparison testing and time-dependent endpoints were based on this subgroup analysis. A sensitivity analysis was also conducted to assess the reason for early relapses in the group of two or more previous DMTs. The second comparison was between patients with specific DMTs before cladribine tablets. In this analysis, glatiramer acetate, interferons and teriflunomide were grouped together as 'platform therapies' and dimethyl fumarate, fingolimod and natalizumab were analyzed separately. The first six months of each patient's washout period were examined for relapses.

3. Results

3.1. Study sample

The study sample included data on 179 patients from 16 of the 21 hospital districts in Finland, who were followed for a median 19.0 months (IQR 12.0-26.2). Follow-up time exceeded 12 months in 134 patients (74.9%) and 24 months in 57 patients (31.8%). Median EDSS at baseline was 2.0 (IQR 1.0-3.0) and mean ARR at baseline was 1.0 (SD 0.89). Demographic details and clinical parameters of the study sample

are presented in Table 1, and comparison between subgroups in Table 2 and Table 3.

A majority of the patients had received previous DMTs prior to cladribine tablets (n=126, 70.4%) (Table 1 and Fig. 1) and approximately half of the cohort had received two or more previous DMTs (n=92, 51.4%). At baseline, patients with two or more previous DMTs were older, had longer disease duration, and slightly higher EDSS when compared to patients with 0-1 previous DMTs prior to cladribine tablets (Table 2). They were also more often relapse-free at baseline and had lower baseline ARR when compared to patients with 0-1 previous DMTs (Table 2).

The most common last preceding DMT was fingolimod (n=33, 26.2%) followed by dimethyl fumarate (DMF) (n=29, 23.0%) and natalizumab (n=20. 15.9%). The reasons for discontinuing last preceding DMTs were inefficacy (n=65), AEs (n=32), anti-John Cunningham virus (anti-JC virus) antibodies (n=9), patient's wish (n=6), pregnancy (n=5), alteration of disease course (n=2), other (n=8), and unknown (n=7). Multiple reasons were reported in some patients. In patients with platform therapies or DMF as their last preceding therapy, the previous therapy was most frequently discontinued due to inefficacy (72.7% and 82.8%, respectively). Fingolimod was most frequently discontinued due to AEs (39.4%) or inefficacy (33.3%), whereas natalizumab was most frequently discontinued due to presence of anti-JC virus antibodies (45.0%). During washout period, relapses were reported in nine patients switching from fingolimod (27.3%), and one patient each switching from platform therapies (3.0%), DMF (3.4%), and natalizumab (5.0%) (Table 3).

3.2. Efficacy

A total of 154 patients (86.0%) remained relapse-free until the end of follow-up. In comparison, 112 of the 134 patients (83.6%) who were followed for at least 12 months remained relapse-free. After initiation of cladribine tablets, 32 relapses were reported in 25 patients (14.0%). Mean ARR was 0.1 during follow-up (SD 0.3) (Table 1). Notably, 49 of the 53 treatment-naive patients (92.5%) remained relapse-free until the end of follow-up, and mean ARR in treatment-naive patients was 0.1 (SD 0.2) during follow-up (Table 3). EDSS assessments were available in 116 patients at baseline (EDSS 2.0, IQR 1.0-3.0) and 55 patients at 12 months (EDSS 2.0, IQR 1.0-3.0, n=55). Subgroup analysis of EDSS scores was not performed due to the small number of patients with sufficient EDSS values during follow-up.

Median time to first relapse was 6.8 months (IQR 1.3-12.2) and was shorter in patients with two or more previous DMTs (median 2.5 months, IQR 0.6-9.3) when compared to patients with 0-1 previous DMTs (median 11.4 months, IQR 8.7-13.1) (Table 2, Fig. 2, log-rank test, p=0.013). Patients who had switched from fingolimod had a particularly short time to first relapse (median 1.3 months, IQR 0.6-2.7, Table 3). Also, of the 12 patients (6.7%) who experienced an early relapse within the first six months of follow-up, eight (66.7%) had switched from fingolimod. In contrast, only one of these patients (8.3%)

Table 1
Demographic details and clinical parameters of the study cohort.

	All patients n=179	
Before cladribine tablets initiation		
Sex category, n (%)		
Female	153	(85.5)
Male	26	(14.5)
Age, years, mean (SD)		
at diagnosis of MS	29.6	(8.46)
at cladribine tablets initiation	35.9	(9.86)
Disease duration, years, median [Q1, Q3]	4.2	[0.3, 11.2]
Course of disease, n (%)		
RRMS	177	(98.9)
SPMS	2	(1.1)
Number of previous DMTs, n (%)		
0	53	(29.6)
1	34	(19.0)
2	34	(19.0)
3 or more	58	(32.4)
EDSS at baseline, median [Q1, Q3]	2.0	[1.0, 3.0]
Relapses at baseline[a], n (%)		
No relapses	59	(33.0)
1 relapse	71	(39.7)
2 or more relapses	49	(27.4)
ARR at baseline[a], mean (SD)	1.0	(0.89)
After cladribine tablets initiation		
Relapses during follow-up, n (%)		
No relapses	154	(86.0)
1 relapse	18	(10.1)
2 relapses	7	(3.9)
ARR at follow-up, mean (SD)		
at entire follow-up	0.1	(0.3)
at 0-12 mo	0.1	(0.4)
at 12-24 mo	0.1	(0.2)
Time to first relapse[b], mo, median [Q1, Q3]	6.8	[1.3, 12.2]
Number of patients discontinuing cladribine tablets, n (%)	9	(5.0)

[a] During the last 12 months before initiation of cladribine tablets.
[b] In patients with relapses during follow-up.

Table 2
Patients stratified into two groups according to the number of previous disease-modifying therapies.

	0-1 previous DMTs n = 87		2 or more previous DMTs n = 92		p
Before cladribine tablets initiation					
Sex category female, n (%)	76	(87.4)	77	(83.7)	0.550
Age at cladribine tablets initiation, years, mean (SD)	33.5	(8.73)	38.2	(10.35)	0.007
Disease duration, years, median [Q1, Q3]	0.3	[0.2, 2.9]	9.5	[5.7, 14.0]	<0.001
Reason for discontinuing last preceding DMT, n (%)					
Inefficacy	26	(76.5)[a]	39	(42.4)	
Adverse events	4	(11.8)[a]	28	(30.4)	
JC virus	2	(5.9)[a]	7	(7.6)	
Patient's wish	1	(2.9)[a]	5	(5.4)	
Pregnancy	2	(5.9)[a]	3	(3.3)	
Alteration of disease course	1	(2.9)[a]	1	(1.1)	
Other or unknown	2	(5.9)[a]	12	(13)	
EDSS at baseline, median [Q1, Q3]	1.5	[1.0, 2.5]	2.0	[1.5, 3.5]	0.028
Relapses at baseline[b], n (%)					<0.001
No relapses	17	(19.5)	42	(45.7)	
1 relapse	36	(41.4)	35	(38.0)	
2 or more relapses	34	(39.1)	15	(16.3)	
ARR at baseline[b], mean (SD)	1.3	(0.89)	0.7	(0.81)	<0.001
After cladribine tablets initiation					
Relapses during follow-up, n (%)					0.031
No relapses	80	(92.0)	74	(80.4)	
1 relapse	7	(8.0)	11	(12.0)	
2 relapses	–		7	(7.6)	
ARR at follow-up, mean (SD)					
at entire follow-up	0.1	(0.18)	0.2	(0.38)	0.063
at 0-12 mo	0.1	(0.2)	0.2	(0.5)	0.063
at 12-24 mo	0.0	(0.2)	0.1	(0.3)	0.550
Time to first relapse[c], mo, median [Q1, Q3]	11.4	[8.7, 13.1]	2.5	[0.6, 9.3]	0.013
Number of patients discontinuing cladribine tablets, n (%)	2	(2.3)	7	(7.6)	0.208

[a] In the group of patients with 0-1 previous DMTs, the proportion displayed here is relative to patients with one previous DMT (n=34) and not the whole group.
[b] During the last 12 months before initiation of cladribine tablets.
[c] In patients with relapses during follow-up.

Table 3
Comparison between patients switching from the most common previous disease-modifying therapies as well as treatment-naive patients. The table does not represent the entire cohort, as patients switching from other disease-modifying therapies (alemtuzumab [n=6], daclizumab [n=1], ocrelizumab [n=3], and rituximab [n=1]) are not shown. For clarity, null values are not shown.

Last preceding DMT before cladribine tablets	Platform therapies[a]		Dimethyl fumarate		Fingolimod		Natalizumab		Treatment-naive	
	n = 33		n = 29		n = 33		n = 20		n = 53	
Before cladribine tablets initiation										
Sex category female, n (%)	27	(81.8)	22	(75.9)	27	(81.8)	17	(85.0)	50	(94.3)
Age at cladribine tablets initiation, years, mean (SD)	37.4	(10.39)	35.3	(8.41)	38.9	(10.48)	37.4	(11.83)	33	(9.17)
Disease duration, years, median [Q1, Q3]	7.2	[3.1, 10.1]	3.5	[2.3, 10.4]	11.2	[5.9, 13.8]	7.9	[4.6, 14.7]	0.2	[0.1, 0.3]
Number of previous DMTs, n (%)										
1	11	(33.3)	14	(48.3)	1	(3.0)	7	(35.0)	–	
2 or more	22	(66.7)	15	(51.7)	32	(96.7)	13	(65.0)	–	
Reason for discontinuing last preceding DMT, n (%)										
Inefficacy	24	(72.7)	24	(82.8)	11	(33.3)	3	(15.0)	–	
Adverse events	8	(24.2)	4	(13.8)	13	(39.4)	3	(15.0	–	
JC virus	–	–	–	–	–		9	(45.0)	–	
Patient's wish	1	(3.0)	1	(3.4)	2	(6.1)	2	(10.0)	–	
Pregnancy	–		–		3	(9.1)	2	(10.0)	–	
Alteration of disease course	–		–		–		2	(10.0)	–	
Other or unknown	1	(3.0)	1	(3.4)	4	(12.1)	5	(25.0)	–	
Washout from previous DMT, mo, median [Q1, Q3]	1.6	[0.7, 3.0]	0.9	[0.2, 2.1]	3.1	[2.2, 4.8]	3.1	[1.3, 6.3]	–	
Patients with relapses during washout[b], n (%)	1	(3.0)	1	(3.4)	9	(27.3)	1	(5.0)	–	
EDSS at baseline, median [Q1, Q3]	1.5	[1.0, 2.2]	2.5	[1.8, 4.0]	2.0	[2.0, 2.5]	2.2	[1.0, 3.8]	1.5	[0.2, 2.0]
Relapses at baseline[c], n (%)										
No relapses	11	(33.3)	12	(41.4)	13	(39.4)	15	(75.0)	2	(3.8)
1 relapse	17	(51.5)	11	(37.9)	13	(39.4)	5	(25.0)	20	(37.7)
2 or more relapses	5	(15.2)	6	(20.7)	7	(21.2)	–		31	(58.5)
ARR at baseline[c], mean (SD)	0.8	(0.76)	0.8	(0.77)	0.9	(0.89)	0.2	(0.44)	1.7	(0.77)
After cladribine tablets initiation										
Relapses during follow-up, n (%)										
No relapses	30	(90.9)	25	(86.2)	23	(69.7)	17	(85.0)	49	(92.5)
1 relapse	3	(9.1)	2	(6.9)	7	(21.2)	1	(5.0)	4	(7.5)
2 relapses	–		2	(6.9)	3	(9.1)	2	(10.0)	–	
ARR at entire follow-up, mean (SD)	0.1	(0.22)	0.2	(0.41)	0.2	(0.37)	0.2	(0.42)	0.1	(0.20)
Time to first relapse[d], mo, median [Q1, Q3]	6.8	[3.6, 15.8]	5.7	[2.4, 10.3]	1.3	[0.6, 2.7]	7.4	[5.5, 16.6]	11.8	[10.8, 12.6]
Patients discontinuing cladribine tablets, n (%)	–		1	(3.4)	6	(18.2)	1	(5.0)	1	(1.9)

[a] Glatiramer acetate (n=7), interferons (n=13) and teriflunomide (n=13).
[b] The first six months of each patient's washout period were examined for relapses.
[c] During the last 12 months before initiation of cladribine tablets.
[d] In patients with relapses during follow-up.

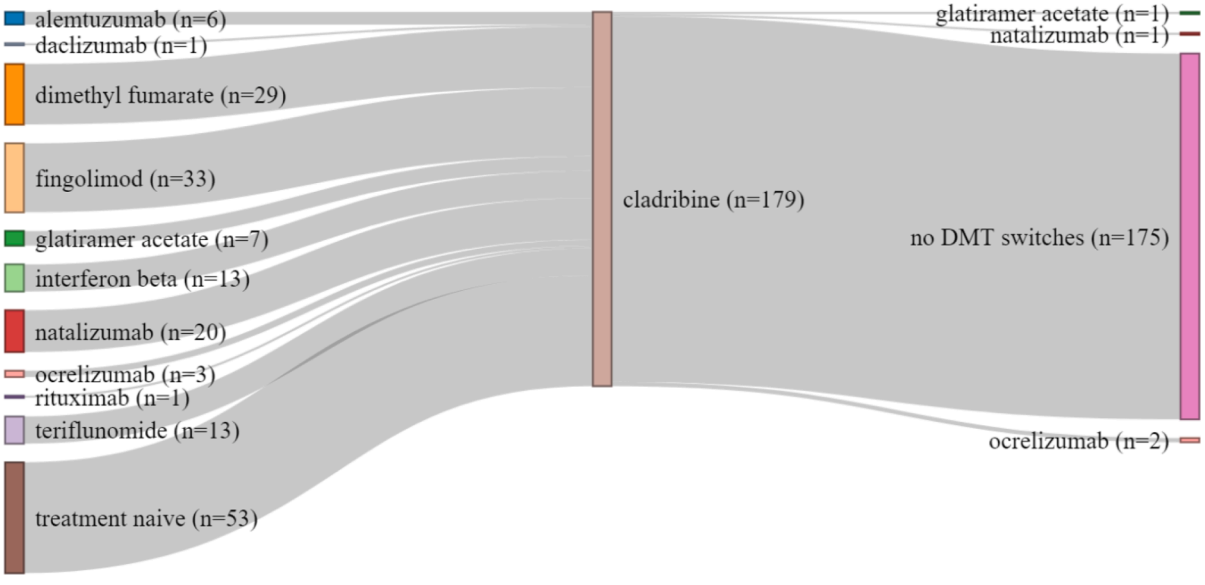

Fig. 1. Treatment sequencing before and after cladribine tablets. Last preceding therapies are presented on the left. Subsequent therapies after a treatment switch are presented on the right.

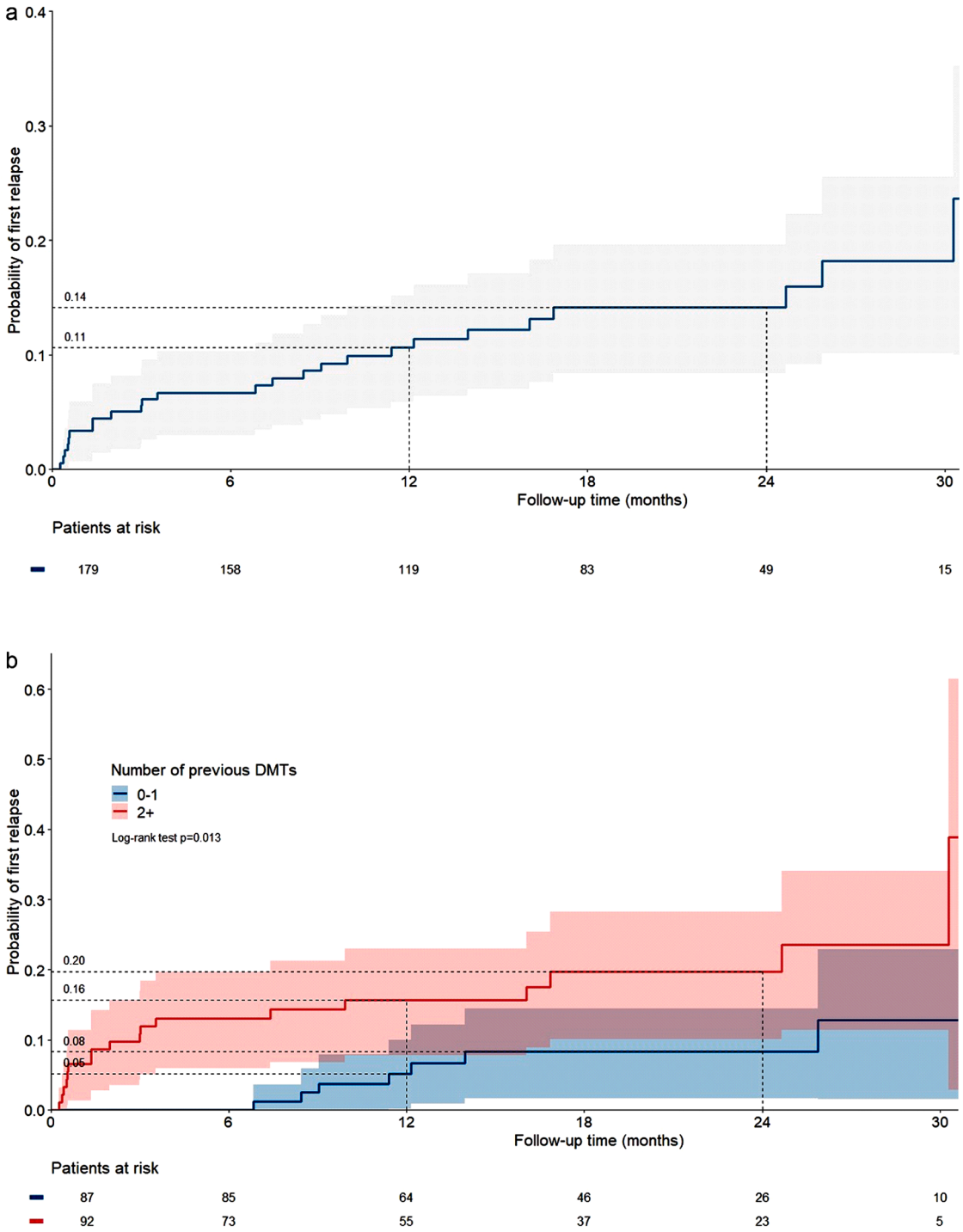

Fig. 2. A cumulative events curve displaying probability of first relapse (and 95% confidence intervals) during follow-up: a) all patients, b) according to the number of previous disease-modifying therapies (DMTs)

Table 4
Adverse events reported during follow-up. For clarity, proportions are not shown in categories with only 1 patient (0.6%).

	Patients with event	
	n	%
Any adverse event	30	16.8
Infections and infestations		
Herpetic skin infection	8	4.5
Herpes simplex	7	3.9
Herpes zoster	1	
Non-herpetic skin or mucocutaneous infection[a]	5	2.8
Upper respiratory infection	5	2.8
Unspecified infection	1	
Urinary tract infection	1	
Vaginal infection	1	
Nervous system disorders		
Headache	14	7.8
Dysesthesia	1	
Gastrointestinal disorders		
Nausea	7	3.9
Abdominal pain	2	1.1
Diarrhea	2	1.1
Dyspepsia	1	
Skin disorders		
Alopecia	2	1.1
Acne	1	
Dermatitis	1	
General disorders		
Malaise	2	1.1
Musculoskeletal disorders		
Back pain	2	1.1
Cardiovascular disorders		
Cardiac arrest	1	
Hepatobiliary disorders		
Hepatitis[b]	1	
Psychiatric disorders		
Insomnia	1	

[a] Non-herpetic skin or mucocutaneous infection includes terms abscess, furunculus, ringworm, and tinea pedis.
[b] Etiology of hepatitis is not reported.

had switched from natalizumab. To test the impact of a possible disease reactivation effect after fingolimod, all patients switching from fingolimod (n=33) were excluded, after which there was no difference in the time to first relapse between patients with 0-1 and two or more previous DMTs (p=0.252, data not shown).

3.3. Safety

3.3.1. Adverse events

A total of 61 AEs were reported in 30 patients (16.8%) (Table 4). The most frequent AEs were headache (n=14, 7.8%), *Herpes simplex* (n=7, 3.9%), and nausea (n=7 patients 3.9%). Only one *Herpes zoster* infection (0.6%) was reported in a patient who switched from natalizumab to cladribine tablets. In addition to herpetic infections, seven other AEs suggestive of representing skin or mucocutaneous infections (abscess, furunculus, ringworm, and tinea pedis) were reported in altogether seven patients (3.9%), although the site of these infections was not specified. Notably, a single case of unspecified hepatitis was reported (0.6%). One patient died of cardiac arrest 1.4 years after the second-year dosing of cladribine tablets.

3.3.2. Lymphocytes

ALCs were available in 166 patients (92.7%). Of these patients, 29 (17.5%) had grade I, 58 (34.9%) grade II, and 37 (22.3%) grade III lymphopenia at any point during follow-up. No grade IV lymphopenia was recorded. Before the second-year dosing at 12 months, 7/95 (7.4%) patients had an ALC lower than 0.8 10^9/L (Fig. 3).

ALCs remained within normal limits in 42 (25.3%) patients. To investigate whether clinical efficacy was altered in this population, an additional descriptive analysis on relapse rates was performed. Five of these patients (11.9%) experienced a relapse during follow-up, and mean ARR in patients without lymphopenia was 0.1 (SD 0.3), thus being in line with the total cohort.

3.4. Treatment discontinuation and subsequent therapies

Cladribine tablets were discontinued in nine patients (5.0%), seven of whom had used two or more previous DMTs before cladribine tablets. Reasons for treatment discontinuation were variable. These included: AEs (n=2); inefficacy (n=2); change of diagnosis (n=1); death (n=1); medication to a comorbidity (n=1); and unknown (n=2). The two AEs resulting in discontinuation included lymphopenia and lymphopenia together with hepatitis. One patient was diagnosed with an autoimmune comorbidity, which required treatment with another immunosuppressive agent, leading to the termination of cladribine tablets after the first year of treatment.

Discontinuation was most common among patients who had switched from fingolimod to cladribine tablets (n=6/33, 18.2%) (Table 3). However, no common cause for discontinuation could be identified among these patients (data not shown). After treatment discontinuation, a subsequent DMT was initiated in four patients (2.2%). These patients had discontinued cladribine tablets during their first (n=2), second (n=1), or third (n=1) treatment year. The subsequent DMTs included ocrelizumab (n=2), glatiramer acetate (n=1), and natalizumab (n=1) (Fig. 1).

4. Discussion

In this nationwide real-world study, we used data from the Finnish MS registry to describe the demographic details and clinical outcomes of 179 patients treated with cladribine tablets in Finland. After the initiation of cladribine tablets, mean ARR was 0.1 during a median follow-up of 19.0 months. For comparison, in the clinical CLARITY trial, ARR was 0.14 during a 96-week study, whereas in a previous real-world study, ARR was 0.31 during a median follow-up of 3.5 years (Giovannoni et al., 2010; Lizak et al., 2021). The higher ARR observed in the real-world study by Lizak et al. may reflect differences in follow-up times and baseline characteristics between studies. Also, the majority of patients had received only their first year dose of cladribine, which may influence efficacy outcomes (Lizak et al., 2021).

In the present study, patients initiating cladribine tablets for MS were characterized by a high female to male ratio in contrast to previous cohorts (Bose et al., 2021; Lizak et al., 2021; Pfeuffer et al., 2021; Rolfes et al., 2021). The reason for the relative paucity of male individuals especially among treatment naive patients in this cohort is unknown. Cultural or family planning preferences may attribute to this finding. Two distinct subgroups could be identified according to previous DMT use. Approximately half of the patients were either naive to treatment or had used one previous DMT, while the rest had used two or more previous DMTs before switching to cladribine tablets. Patients with two or more previous DMTs had a more advanced disease in contrast to patients with 0-1 previous DMTs, characterized by longer disease duration, less relapses, and slightly higher EDSS before switching to cladribine tablets. These findings are not unexpected, as they reflect not only the natural course of MS, but also current treatment guidelines and reimbursement criteria.

In Finland, reimbursement criteria for the use of cladribine tablets are in line with the therapeutic indication evaluated by the European Medicines Agency (European Medicines Agency, 2021). Treatment-naive patients are entitled to full reimbursement of cladribine tablets if they have experienced at least two relapses within one year and have inflammatory findings in an MRI, whereas patients switching from other therapies may be entitled to full reimbursement despite being relapse-free in case of an inflammatory MRI finding while

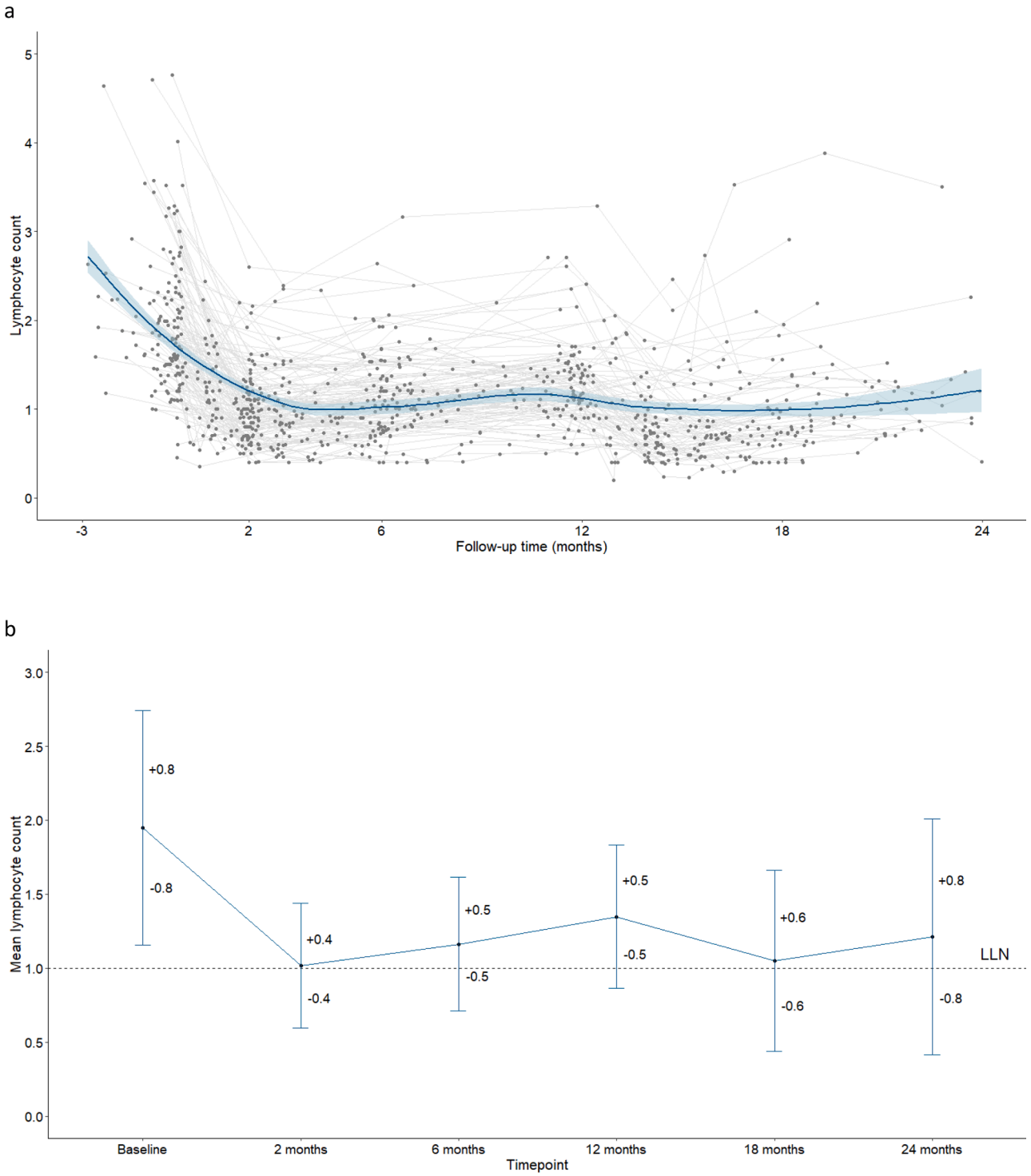

Fig. 3. Mean absolute lymphocyte counts (10^9/L) before and after initiation of cladribine tablets: a) absolute values, b) means and standard deviations at time points of special interest. LLN = Lower Limit of Normal

on previous DMT. In light of these stringent reimbursement criteria, it is surprising that 33% of the patients in our cohort were relapse-free during the year before treatment initiation. This may be explained by clinically stable patients switching therapies due to tolerability issues, family planning, presence of anti-JC virus antibodies, or radiological disease activity.

Patients with two or more previous DMTs had a shorter time to first relapse when compared to patients who were treatment-naive or had used one previous DMT. The former group has not been investigated in clinical trials, therefore giving new information on the outcomes of cladribine tablet use in a real-world setting. In patients with two or more previous DMTs, time to first relapse was very short (median 2.5 months). This effect was shown to be driven by early relapses in patients switching from fingolimod to cladribine tablets, likely representing disease reactivation or rebound after fingolimod. This is not entirely unexpected, as disease reactivation after fingolimod discontinuation has been reported (Barry et al., 2019). There are few previous reports on patients switching from fingolimod to cladribine tablets, including

description of cases with disease reactivation (Coss-Rovirosa et al., 2020; Prosperini et al., 2019).

Interestingly, while patients switching from fingolimod seemed to be at risk for disease reactivation both during washout and after the switch, few patients switching from natalizumab showed signs of clinical disease activity despite similar washout period lengths. The number of patients in each subgroup was small and follow-up time was limited, and therefore, any conclusions should be made with caution. Although discontinuation of natalizumab has been associated with an increased risk for relapses or disease reactivation (Mustonen et al., 2020; Prosperini et al., 2019), conflicting results have been published on the occurrence of disease reactivation when switching from natalizumab to cladribine tablets (Möhn et al., 2019; Pfeuffer et al., 2021). In our cohort, the most common reason for discontinuing natalizumab was the presence of anti-JC virus antibodies. Nevertheless, disease reactivation has also been shown to occur in patients discontinuing natalizumab due to presence of anti-JC virus antibodies, as shown in an observational study comparing rituximab and fingolimod after natalizumab (Alping et al., 2016).

The most frequently reported AE was headache, which is in line with the findings from the clinical trial program (Cook et al., 2019; Giovannoni et al., 2010). A recent prospective bicentric cohort study reported skin reactions to be common after cladribine tablets (Rolfes et al., 2021). In our study, skin disorders including alopecia, acne, and dermatitis were reported in five patients (2.8%). Furthermore, seven patients (3.9%) experienced AEs which could be categorized as non-herpetic skin or mucocutaneous infections, although the site of infection in these AEs was not reported. One case of hepatitis was reported, which is interesting, as hepatobiliary disorders have also been reported in the clinical trials (Giovannoni et al., 2010; Montalban et al., 2018). We also report one fatality in a patient who died of cardiac arrest 1.4 years after the last dose of cladribine tablets.

Most patients experienced mild or moderate lymphopenia. Grade III lymphopenia was detected in 22.3% of the patients, which is similar to the 25% observed at any time during the clinical trials (Cook et al., 2019). Also, no grade IV lymphopenia was recorded, in contrast to the <1% of recorded cases in the clinical trial program (Cook et al., 2019). Most patients' lymphocytes recovered before the second-year dose of cladribine tablets. A small subgroup of patients had no reduction in ALCs. Nevertheless, clinical outcomes of these patients were comparable to the total cohort. This is not unexpected, as the mode of action of cladribine has been linked to the kinetics of specific subtypes of lymphocytes rather than total lymphocyte numbers (Baker et al., 2017; Comi et al., 2019; Stuve et al., 2019).

The strengths of the present study include the relatively large sample size and the good national coverage of the Finnish MS registry. Our cohort represents real-world MS patients treated at both secondary and tertiary centers in Finland. These types of cohort studies provide unique insights into diverse populations, including patients with different ethnic or genetic backgrounds, variable comorbidities, and previous exposure to multiple DMTs – in contrast to clinical trials – where stringent inclusion and exclusion criteria may limit generalizability. However, due to its non-randomized setting, the present study is not optimal for assessing efficacy outcomes, and regression to mean may affect relapse outcomes. EDSS data during follow-up were limited, and therefore, conclusions about long-term disability outcomes could not be made. Other limitations include the possibility of missing data due to the voluntary nature in which data entries to the Finnish MS registry are made, as well as the lack of MRI data.

In conclusion, this registry study demonstrated that approximately half of the patients initiating cladribine tablets in Finland had used two or more previous DMTs before switching to cladribine. These patients had a particularly short time to first relapse, driven mostly by early relapses experienced by patients switching from fingolimod, and likely representing rebound after fingolimod. However, ARR during follow-up was low in the total cohort. Headache was the most frequent AE. Overall, these data support the findings from clinical trials on the clinical outcomes and safety of cladribine tablets in a real-life setting.

Funding

This study was funded by Merck Oy, Espoo, Finland, an affiliate of Merck KGaA (CrossRef Funder ID: 10.13039/100009945). The funding included data collection and analysis. EJ is an employee of Merck Oy. IR received a consultancy fee from Merck Oy for the preparation of the first version of this manuscript and used his personal research grant from the Pirkanmaa Regional Fund of The Finnish Cultural Foundation (grant 50211598) to work on the final version of this manuscript. MV, HK, SA, JOTS, MR, and MS-H received no funding in the context of this study.

CRediT authorship contribution statement

Ilkka Rauma: Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Matias Viitala:** Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Hanna Kuusisto:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Sari Atula:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Jussi O T Sipilä:** Methodology, Investigation, Writing – review & editing. **Mervi Ryytty:** Methodology, Investigation, Writing – review & editing. **Merja Soilu-Hänninen:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Elina Järvinen:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

IR has received research grants from The Finnish Medical Foundation, The Finnish MS Foundation, The Hospital District of South Ostrobothnia, the Orion Research Foundation sr, and the Pirkanmaa Regional Fund of The Finnish Cultural Foundation; a consultancy fee from Merck; support for meetings and/or travel from Novartis, Sanofi Genzyme, and Teva; and honoraria for lectures or for serving as an investigator in clinical trials from Novartis and Sanofi. MV has nothing to disclose. HK has received honoraria for lectures, advisory boards or for serving as an investigator for clinical trials from Biogen, BMS, Celgene, Novartis, Merck, Roche, and Sanofi. SA has received support for meetings and/or travel from Merck; and honoraria for lectures or for serving as an investigator in a clinical trial from Novartis, Merck, Biogen, and Roche. JOTS has received research grants from The Finnish Parkinson Foundation and Maire Jokinen Foundation; support for meetings and travel from the Finnish Neurological Association; honorarium for participating in an advisory board from Medaffcon; and holds Orion Corporation shares. MR has received honoraria for lectures, advisory boards or for serving as an investigator in clinical trials from Biogen, Celgene, Merck, Novartis, Roche, Sanofi, and Teva. MS-H has received honoraria for lectures, advisory boards or for serving as an investigator for clinical trials from Biogen, BMS, Celgene, Genzyme, Novartis, Merck, Roche, Sanofi and Teva. EJ is an employee of Merck Oy, Espoo, Finland, an affiliate of Merck KGaA.

Acknowledgements

The authors would like to thank Eemil Karttunen for checking the language of the manuscript.

References

Alping, P., Frisell, T., Novakova, L., Islam-Jakobsson, P., Salzer, J., Björck, A., Axelsson, M., Malmeström, C., Fink, K., Lycke, J., Svenningsson, A., Piehl, F., 2016. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann. Neurol. 79, 950–958. https://doi.org/10.1002/ana.24651.

Baker, D., Herrod, S.S., Alvarez-Gonzalez, C., Zalewski, L., Albor, C., Schmierer, K., 2017. Both cladribine and alemtuzumab may effect MS via B-cell depletion. Neurol. - Neuroimmunol. Neuroinflammation 4, e360. doi:10.1212/NXI.0000000000000360.

Barry, B., Erwin, A.A., Stevens, J., Tornatore, C., 2019. Fingolimod Rebound: A Review of the Clinical Experience and Management Considerations. Neurol. Ther. 8, 241–250. https://doi.org/10.1007/s40120-019-00160-9.

Bose, G., Rush, C., Atkins, H.L., Freedman, M.S., 2021. A real-world single-centre analysis of alemtuzumab and cladribine for multiple sclerosis. Mult. Scler. Relat. Disord. 52, 102945 https://doi.org/10.1016/j.msard.2021.102945.

Ceronie, B., Jacobs, B.M., Baker, D., Dubuisson, N., Mao, Z., Ammoscato, F., Lock, H., Longhurst, H.J., Giovannoni, G., Schmierer, K., 2018. Cladribine treatment of multiple sclerosis is associated with depletion of memory B cells. J. Neurol. 265, 1199–1209. https://doi.org/10.1007/s00415-018-8830-y.

Comi, G., Cook, S., Giovannoni, G., Rieckmann, P., Sørensen, P.S., Vermersch, P., Galazka, A., Nolting, A., Hicking, C., Dangond, F., 2019. Effect of cladribine tablets on lymphocyte reduction and repopulation dynamics in patients with relapsing multiple sclerosis. Mult. Scler. Relat. Disord. 29, 168–174. https://doi.org/10.1016/j.msard.2019.01.038.

Cook, S., Leist, T., Comi, G., Montalban, X., Giovannoni, G., Nolting, A., Hicking, C., Galazka, A., Sylvester, E., 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.

Coss-Rovirosa, F., Salado-Burbano, J., Casallas-Vanegas, A., Caire-Herrera, L.E., Gómez-Figueroa, E., Flores-Rivera, J., 2020. Severe fingolimod rebound syndrome after switching to cladribine treatment. Mult. Scler. Relat. Disord. 40, 101938 https://doi.org/10.1016/j.msard.2020.101938.

European Medicines Agency, 2021. MAVENCLAD EU Summary of Product Characteristics [WWW Document]. URL https://www.ema.europa.eu/en/documents/product-information/mavenclad-epar-product-information_en.pdf (accessed 9.14.21).

Giovannoni, G., Comi, G., Cook, S., Rammohan, K., Rieckmann, P., Sørensen, P.S., Vermersch, P., Chang, P., Hamlett, A., Musch, B., Greenberg, S.J., 2010. A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. N. Engl. J. Med. 362, 416–426. https://doi.org/10.1056/NEJMoa0902533.

Giovannoni, G., Soelberg Sorensen, P., Cook, S., Rammohan, K., Rieckmann, P., Comi, G., Dangond, F., Adeniji, A.K., Vermersch, P., 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. J. 24, 1594–1604. https://doi.org/10.1177/1352458517727603.

Laakso, S.M., Viitala, M., Kuusisto, H., Sarasoja, T., Hartikainen, P., Atula, S., Tienari, P. J., Soilu-Hänninen, M., 2019. Multiple sclerosis in Finland 2018—Data from the national register. Acta Neurol. Scand. 140, 303–311. https://doi.org/10.1111/ane.13145.

Lizak, N., Hodgkinson, S., Butler, E., Lechner-Scott, J., Slee, M., McCombe, P.A., Shaw, C., Skibina, O., Vucic, S., Shuey, N., Barnett, M.H., Parratt, J., Butzkueven, H., Jack, D., Fabris, J., Kalincik, T., 2021. Real-world effectiveness of cladribine for Australian patients with multiple sclerosis: An MSBase registry substudy. Mult. Scler. J. 27, 465–474. https://doi.org/10.1177/1352458520921087.

Möhn, N., Skripuletz, T., Sühs, K.-W., Menck, S., Voß, E., Stangel, M., 2019. Therapy with cladribine is efficient and safe in patients previously treated with natalizumab. Ther. Adv. Neurol. Disord. 12, 175628641988759 https://doi.org/10.1177/1756286419887596.

Montalban, X., Leist, T.P., Cohen, B.A., Moses, H., Campbell, J., Hicking, C., Dangond, F., 2018. Cladribine tablets added to IFN-β in active relapsing MS. Neurol. - Neuroimmunol. Neuroinflammation 5, e477. https://doi.org/10.1212/NXI.0000000000000477.

Mustonen, T., Rauma, I., Hartikainen, P., Krüger, J., Niiranen, M., Selander, T., Simula, S. S., Remes, A.M., Kuusisto, H., 2020. Risk factors for reactivation of clinical disease activity in multiple sclerosis after natalizumab cessation. Mult. Scler. Relat. Disord. 38, 101498 https://doi.org/10.1016/j.msard.2019.101498.

Patti, F., Visconti, A., Capacchione, A., Roy, S., Trojano, M., 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, 175628642092268 https://doi.org/10.1177/1756286420922685.

Pfeuffer, S., Rolfes, L., Hackert, J., Kleinschnitz, K., Ruck, T., Wiendl, H., Klotz, L., Kleinschnitz, C., Meuth, S.G., Pul, R., 2021. Effectiveness and safety of cladribine in MS: Real-world experience from two tertiary centres. Mult. Scler. J. https://doi.org/10.1177/13524585211012227, 135245852110122.

Pirttisalo, A., Soilu-Hänninen, M., Sumelahti, M., Krökki, O., Murtonen, A., Hänninen, K., Sipilä, J.O.T., 2020. Changes in multiple sclerosis epidemiology in Finland over five decades. Acta Neurol. Scand. 142, 200–209. https://doi.org/10.1111/ane.13295.

Prosperini, L., Kinkel, R.P., Miravalle, A.A., Iaffaldano, P., Fantaccini, S., 2019. Post-natalizumab disease reactivation in multiple sclerosis: systematic review and meta-analysis. Ther. Adv. Neurol. Disord. 12, 175628641983780 https://doi.org/10.1177/1756286419837809.

Rolfes, L., Pfeuffer, S., Hackert, J., Pawlitzki, M., Ruck, T., Sondermann, W., Korsen, M., Wiendl, H., Meuth, S.G., Kleinschnitz, C., Pul, R., 2021. Skin Reactions in Patients With Multiple Sclerosis Receiving Cladribine Treatment. Neurol. - Neuroimmunol. Neuroinflammation 8, e990. https://doi.org/10.1212/NXI.0000000000000990.

Stuve, O., Soelberg Soerensen, P., Leist, T., Giovannoni, G., Hyvert, Y., Damian, D., Dangond, F., Boschert, U., 2019. Effects of cladribine tablets on lymphocyte subsets in patients with multiple sclerosis: an extended analysis of surface markers. Ther. Adv. Neurol. Disord. 12, 175628641985498 https://doi.org/10.1177/1756286419854986.

U.S. Department of Health and Human Services, National Institutes of Health, N.C.I., 2017. Common Terminology Criteria for Adverse Events v5.0 [WWW Document]. URL https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.