Aus der

Neurologischen Universitätsklinik Tübingen

A retrospective data analysis of multiple sclerosis (MS) patients under the disease-modifying treatment of cladribine: Assessing effectiveness and side effects in a real-world cohort

Inaugural Dissertation
zur Erlangung des Doktorgrades
der Medizin

der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen

vorgelegt von

Woitschach, Lara Heike Isabella

2026

Dekan:	Professor Dr. B. Pichler
1. Berichterstatter:	Professor Dr. M. C. Kowarik
2. Berichterstatter:	Professor Dr. J. Henes

Tag der Disputation: 19.12.2024

Dedication

I would like to start by thanking apl. Prof. Dr. Markus Kowarik, who has been a constant support and advised me in the organisation, conduction and analysis of the study. Furthermore, I would like to thank Dr med. Christoph Ruschil for his invaluable assistance in planning and organising the project.

Moreover, I am extremely grateful to Michael Ernst, an established neurologist who has been a constant source of support throughout the project. I would also like to thank the other neurologists, namely Dr. med. Benedicta Kühnler, Dr. med. Sylke Schlemilch-Paschen, Dr. med Lukas Cepek and Dr. med. Daniela Rau who provided the data and helped me merge it.

Finally, I would like to thank Dr. Marina Pumptow for her consultation regarding the statistical analysis.

Index

List of Abbreviations

MS	Multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
PPMS	Primary progressive multiple sclerosis
SPMS	Secondary progressive multiple sclerosis
CNS	Central nervous system
EMA	European Medicines Agency
MRI	Magnetic resonance imaging
EDSS	Expanded disability status scale
DMT	Disease modifying therapy
DMF	Dimethyl fumarate
IQR	Interquartile range
CI	Confidence interval

List of Tables

List of Figures

1. Introduction

Multiple sclerosis is the most prevalent non-traumatic disabling disease in young adults, affecting the central nervous system (CNS). The disease, preferably occurring in female young adults distant from the equator, shows a worldwide increase of both prevalence and incidence. Although the underlying cause of MS is not yet discovered, interactions between genes and environment are believed to play an important role in the development of the disease [Yamout et al., 2018]; [Dobson et al., 2019].

Multiple sclerosis, which is considered as an autoimmune disease, is characterized by inflammatory lesions that contain T-Lymphocytes, B-Lymphocytes and other immune cells. Consequently, oligodendrocyte damage with demyelination as well as axonal damage in a later stage emerge and may lead to various clinical symptoms [Dobson et al., 2019]; [Leist et al., 2014]. Relapsing-remitting multiple sclerosis (RRMS) is the most common form of the disease, characterized by recurring clinical symptoms. If left untreated, RRMS progresses to secondary progressive multiple sclerosis (SPMS) in about 50% of cases, causing a gradual deterioration over many years. Primary progressive multiple sclerosis (PPMS), which has a progressive disease course from the beginning, is less common, occurring in only 15% of cases [Correale et al., 2017]; [Doshi et al., 2016].

Multiple sclerosis is diagnosed based on clinical relapses and cerebrospinal fluid analysis and MRI (Magnetic resonance imaging) by demonstrating dissemination in space and time, as per the 2017 revised McDonald's criteria [Thompson et al., 2018]; [Dobson et al., 2019].

Although multiple sclerosis is still incurable nowadays, there’s an emerge of effective disease-modifying therapies that can favorably impact long-term outcomes, as well as reduce the rate of relapses and limit the accumulation of MRI lesions. Based on their efficacy, the above DMTs are stratified into platform therapy (e.g. beta interferon, dimethyl fumarate, glatiramer acetate, teriflunomide) and high efficacy therapy (cladribine, fingolimod, natalizumab, ocrelizumab, alemtuzumab). In the past, therapies were categorized as either immunosuppressive or immunomodulatory. However, with the introduction of

alemtuzumab and cladribine, a new treatment concept has emerged: immune reconstitution therapy. This therapy is targeted at sustained immunological effects and can therefore be administered as a short course. Hence, cladribine plays an important role in current multiple sclerosis treatment [Yamout et al., 2018]; [Dobson et al., 2019]; [Hauser, 2020]; [Selmaj et al., 2024].

Cladribine (Mavenclad®) was approved by the European Medicines Agency (EMA) in 2017 as the first short-course DMT with an oral application for the disease-modifying therapy of highly active relapsing multiple sclerosis. It is administrated in two short annual treatment courses. As a deoxyadenosine analogue prodrug, it depletes lymphocytes in particular to impair the pathogenesis of multiple sclerosis [Deeks, 2018]; [Moser et al., 2022]; [Comi et al., 2019]; [Giovannoni et al., 2022].

The phase III CLARITY study in 2010 demonstrated that patients treated with cladribine tablets experienced a significantly lower relapse rate, a reduced risk of disability progression, and less MRI activity within 96 weeks of observation. It is worth noting that adverse events, including lymphocytopenia and herpes zoster, occurred more frequently in the cladribine group than in the placebo group [Giovannoni et al., 2010].

Based on these results, the study was extended in 2012, stratifying the patients according to baseline data, including demographics, disease duration, treatment history and disease activity. In conclusion, the study showed that cladribine treatment achieved a constant reduction in annual relapse rate in comparison to the placebo across the entire spectrum of baseline data [Rammohan et al., 2012].

The lasting positive effect on both clinical and MRI outcomes was demonstrated in a follow-up CLARITY Extension study conducted in 2018, with an additional 96 weeks of follow-up. Furthermore, the study concluded that re-treatment after the second course does not provide a huge benefit [Giovannoni et al., 2018].

To further assess the long-term efficacy of cladribine, the eight-year clinical follow-up of cladribine-treated patients from Phase 2 and 3 trials was published in 2020. In conclusion, this study showed a diminished risk of EDSS progression and SP conversion in patients treated with cladribine compared to placebo [Moccia et al., 2020].

In addition, another study published in 2020 evaluated the safety and efficacy of cladribine in long-term treatment. The study included 923 patients from three previous phase III studies (CLARITY, CLARITY extension, and ORACLE-MS) and the prospective PREMIERE registry. The results demonstrated that the addition of further treatment years of observation did not result in a significant alteration of the efficacy and safety outcomes observed in previous studies [Leist et al., 2020].

Results from phase III clinical studies were supported by a 2022 real-world cohort study of 270 patients, which was consistent with the phase III data. Additionally, the study found an increased relapse rate for patients who switched from natalizumab to cladribine, as well as a higher risk of severe lymphopenia for patients who switched from dimethyl fumarate to cladribine [Pfeuffer et al., 2022]. However, further studies are needed to ensure the efficacy and safety of this new treatment.

Although each drug must undergo several phases of clinical examination before being approved for the treatment of multiple sclerosis patients, it is still necessary to further evaluate the efficacy and safety of cladribine in “real-world” clinical use due to several aspects [Rudrapatna et al., 2020].

Since cladribine was approved in 2017, some patients have already completed their fifth year of treatment. This raises the question of whether another course of cladribine should be administered. To answer this question in an evidence-based manner, long-term data from a real-world cohort is required.

Furthermore, clinical studies do not cover the full extent of drug usage or the long-term effects of drug application in real-life scenarios and might also treat defined patient collectives that do not necessarily represent “real-world” patient collectives. As a result, side effects may only manifest after widespread clinical use [Rudrapatna et al., 2020].

As an example daclizumab, which was approved in 2016 for the disease-modifying therapy of multiple sclerosis, was withdrawn in 2018 after eight cases of immune-mediated encephalitis were reported in correlation with its use [Paul-Ehrlich-Institut, 2018].

Regarding the above mentioned reasons, it is of great importance to monitor

cladribine treatment in real-world cohorts in order to detect adverse events in time and to evaluate efficacy across a broad spectrum of patients.

It is also important to consider the prerequisites that make a patient the most suitable for cladribine treatment. The above-mentioned 2022 real-world cohort study has examined the impact of different previous disease-modifying therapies on the outcome of multiple sclerosis and has shown that previous DMTs, as well as several baseline characteristics, play an important role in the disease course [Pfeuffer et al., 2022].

This raises the question of whether there are specific requirements that a patient can meet to achieve the best possible treatment outcome.

Consequently, this thesis evaluates a real-world cohort of patients with relapsing-remitting multiple sclerosis (RRMS) who were treated with cladribine in various treatment centres. The study focuses on efficacy and outcomes, as well as the influence of previous disease-modifying therapies on the disease course, with the aim of identifying characteristics that increase the likelihood of a favourable disease outcome.

2. Methods

2.1 Patient recruitment and ethics

This retrospective multiple center study was performed at the University hospital Tübingen Department of Neurology. The study has been approved by the ethics committee of the Eberhard Karl University Tübingen [Ethics proposal 586/2022BO1] and by the Ärztekammer Baden-Württemberg [B-F-2023-014].

2.2 Data collection

Data were collected from the University Hospital of Tübingen and three established neurological practices in Sinsheim, Stuttgart and Ulm. Multiple sclerosis patients who received cladribine treatment were identified at each site and the diagnosis checked according to the 2017 McDonald criteria. Data from medical records, including age, weight, date of disease diagnosis, information on previous treatments, date of cladribine initiation and adverse events, as well as laboratory results (lymphocytes) and radiological results (T2 lesions on MRI) were collected locally at the above university hospital and at the three neurological practices. Subsequently, the pseudonymized data were transferred to the University hospital of Tübingen and further analysed.

The analysis involves RRMS-patients according to 2017 McDonald criteria who have received cladribine in two treatment cycles in the centres from July 2017 to December 2021, whereat patients with a follow up of less than 18 months were excluded.

2.3 Statistics

Several statistical methods were used to evaluate the data. Descriptive statistics were applied to depict epidemiological data at baseline such as age, gender, weight, disease duration since diagnosis, annual relapse rate, EDSS and MRI progress, number of previous DMTs as well as lymphocyte counts. Regarding lymphocyte counts more detailed, lymphocyte levels were subdivided into three

lymphopenia severity grades corresponding to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
Furthermore, Kaplan-Meier curves were created to assess differences in efficacy outcomes, regarding relapse rates, EDSS and MRI progress, depending on the previous DMT.
All data were non-normally distributed, which required the use of non-parametric tests to detect significance.
In order to ascertain the significance of the efficacy of cladribine on the course of relapse rates and MRI progression, a Wilcoxon test with Bonferroni correction was performed.
In addition to the Kaplan-Meier graphs, a log-rank test was conducted to test for a significant influence of previous DMTs on the time of a first event (relapse, MRI progression, EDSS worsening).
Furthermore, a Cox proportional hazards model was employed to identify both protective and risk factors associated with the disease course of cladribine.

All statistical analysis were executed by using SPSS Statistics 29 (IBM).

3. Results

3.1 Patients

The analysis covers an observation period of 61 months, during which 194 patients were treated in the above-mentioned centres. 15 patients were excluded due to an incomplete second treatment cycle, while another twelve patients were excluded due to loss of follow-up. The remaining 167 patients were further analysed.

3.2 Baseline data

Treatment was administered at four different treatment centres. Out of the 167 patients, 47.9% (80 patients) of the patients received treatment at the neurological practice in Ulm, followed by 22.8% (38 patients) in Stuttgart, 19.8% (33 patients) in Sinsheim, and 9.6% (16 patients) in the university hospital of Tübingen. (Fig. 1)

The duration of the treatment was variable, extending from the second to the seventh year, with the majority of patients in their third year (46 patients, 27.5%), followed by the fourth (39 patients, 23.4%) and fifth (38 patients, 22.8%) years, resulting in a median of four years. (Fig. 2)

The age range of patients in the study was between 19 and 64 years old, with a median age of 34 years. (Fig. 3)

The vast majority of patients were female (132 female patients (79%), 35 male patients (21%)). (Fig. 4)

Notably, 11 patients (6.6%) have already received their third cycle, with two patients receiving it in their fourth year of treatment and nine patients receiving it in their fifth year of treatment.

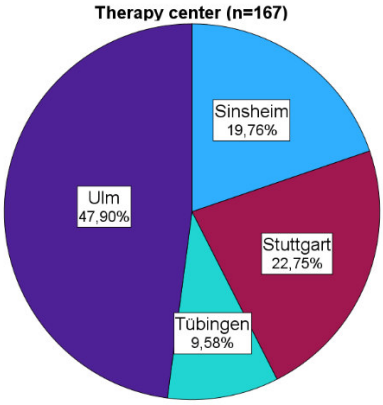


Figure 1 The proportion of treatment centres is shown. Most patients come from Ulm, followed by Stuttgart

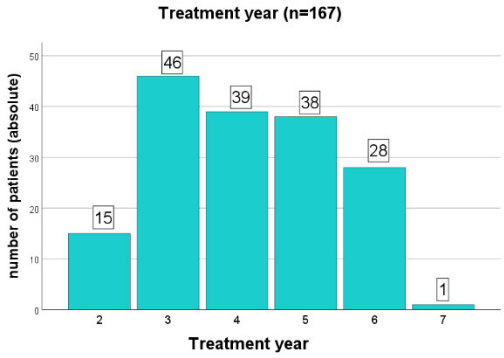


Figure 2 The number of patients (abs) for each year of treatment is shown. Most patients were in the third year of treatment, followed by the fourth and fifth years.

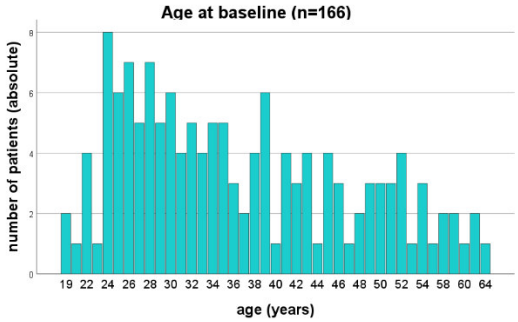


Figure 3 The number of patients in each age group is shown

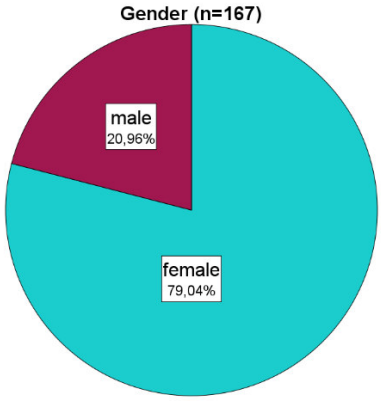


Figure 4 The gender ratio is shown, with women making up a large majority.

3.2.1 Baseline data stratified according to previous DMT

To account for the variability in baseline data between patients with different previous disease-modifying therapies, baseline data were re-evaluated after stratifying patients according to their previous DMTs (Table 1). This resulted in the formation of nine subgroups, including one group of naive patients (n=23, 13.8%), one group with DMT treatment more than 1 year ago (n=18, 10.8%) and seven groups with multiple DMTs within 1 year prior to cladribine initiation. The DMTs used in the study comprised beta-interferon (n=19, 11.4%), dimethyl fumarate (n=39, 23.4%), teriflunomide (n=11, 6.6%), glatiramer acetate (n=12,

7.2%), fingolimod (n=26, 15.6%), natalizumab (n=10, 6.0%) and daclizumab (n=7, 4.2%).

The median age at baseline, which was 34 years in the entire cohort, was further evaluated according to different pre-treatment groups. The youngest baseline age was found in patients previously treated with glatiramer acetate, with a median age of 29 years. This was followed by naive patients with a median age of 31 years, whereas the oldest baseline age was found in patients previously treated with teriflunomide, with a median age of 51 years.

The gender distribution of the entire cohort shows that 79% of the patients were female, indicating a higher proportion of women being treated with cladribine. The data reveals that the highest percentage of women was found among patients who were previously treated with beta-interferon (89.5%) or whose last DMT treatment was more than a year ago (88.9%). On the other hand, the lowest percentage of women was found among patients previously treated with teriflunomide (45.5%) or among naive patients (69.6%). This might be explained by different treatment strategies regarding women of child-bearing age.

There was also a large variation in median weight according to previous DMT. The median weight of the entire cohort was 70kg. Naive patients had the highest weight with a median of 88kg, as well as patients previously treated with natalizumab with a median of 78kg. In contrast, the lowest weight was found in patients previously treated with daclizumab (56.5kg) and patients whose last treatment was more than 1 year ago (63.5kg).

In the overall cohort, the median disease duration from diagnosis to cladribine initiation was 75 months. The time period between diagnosis and initiation of cladribine was shortest in naive patients (2.5 months) and patients previously treated with glatiramer acetate (28.5 months). On the other hand, patients previously treated with natalizumab exhibited the longest time period between disease diagnosis and cladribine initiation (161 months), followed by patients previously treated with fingolimod (117 months).

Regarding outcome measurements, EDSS, ARR and MRI progression were further analysed at baseline.

At baseline, the overall median EDSS was 2. This was also observed in subgroups of patients who had received their last treatment more than a year ago, as well as in patients previously treated with glatiramer acetate and fingolimod. Naive patients and patients previously treated with beta-interferon, dimethyl-fumarate and natalizumab were among the subgroups with lower EDSS scores, with a median EDSS of 1.5. In contrast, the subgroup previously treated with teriflunomide showed the highest EDSS, with a median of 3 (however, this subgroup was older).

The second efficacy parameter is the annual relapse rate, which had an overall median of 1 relapse per year (IQR=0-2). The subgroups with the lowest annual relapse rate were represented by patients previously treated with natalizumab and daclizumab (median ARR= 0, IQR= 0-1). On the contrary, the subgroups with the highest mean annual relapse rate were those who had their last DMT more than a year ago and naive patients, with a median ARR of 2 (IQR= 1-2).

The final efficacy parameter concerns the proportion of patients who showed MRI progression one year before initiation of cladribine - a total of 64.1% of the patients experienced MRI progression at baseline. Subgroups with the lowest proportion of patients showing MRI progression were those previously treated with daclizumab (28.6%) and natalizumab (30%). In contrast, the subgroups with the highest proportion of patients showing MRI progression were those previously treated with glatiramer acetate (91.7%) and treatment-naive patients (87%).

Next, the number of prior DMTs was considered. Overall, the median number of previous disease-modifying therapies was 2 (IQR= 1-2). Besides the subgroup of treatment-naive patients with a median of 0 previous therapies (IQR= 0-0), the lowest number of previous DMTs was found in the subgroups treated with glatiramer acetate, beta-interferon, and dimethyl fumarate (median= 1, IQR= 1-2). The highest number of previous DMTs was found in the subgroup of patients previously treated with daclizumab, with a mean of 3 previous DMTs (IQR= 2-4).

Finally, the median lymphocyte count at baseline was considered. The total median lymphocyte count was 1591 lymphocytes/µl. The lowest median lymphocyte count at baseline was observed in patients previously treated with fingolimod (1170 lymphocytes/µl), followed by patients previously treated with teriflunomide (1340 lymphocytes/µl). In contrast, the highest lymphocyte count was found in patients who had previously received natalizumab treatment (3142 lymphocytes/µl), as well as in treatment-naive patients (2060 lymphocytes/µl).

Table 1: Baseline characteristics of the cohort

	whole cohort	naive	last DMT >1 year ago	beta-interferon	dimethyl fumarate
Patients, abs (rel)	167 (100%)	23 (13.8%)	18 (10.8%)	19 (11.4%)	39 (23.4%)
Age bl (years), median (IQR)	34 (28-44)	31 (24-47)	32.5 (28-39.75)	34 (28-45)	32 (26-42)
Gender f, abs (rel)	132 (79%)	16 (69.6%)	16 (88.9%)	17 (89.5%)	34 (87.2%)
Weight (kg), median (IQR)	70 (62-81.75)	88 (66.5-95,25)	63,5 (58-70.75)	66 (55-78)	70 (63-80)
Disease duration since diagnosis (months), median (IQR)	75 (26.25-130.5)	2.5 (1-4)	88 (43-135)	107 (51-162)	64.5 (45-87)
EDSS bl, median (IQR)	2 (1-3)	1.5 (1-2.375)	2 (1-2.75)	1.5 (1-3.5)	1.5 (1-3)
ARR at bl	1 (0-2)	2 (1-2)	2 (1-2)	1 (0-1)	1 (0-1)
MRI progress bl, abs (rel)	107 (64.1%)	20 (87%)	12 (66.7%)	12 (63.2%)	26 (66.7%)
number of previous DMT, median (IQR)	2 (1-2)	0 (0-0)	2 (1-3)	1 (1-2)	1 (1-2)
0, abs (rel)	23 (13.8%)	23 (100%)	0 (0%)	0 (0%)	0 (0%)
1, abs (rel)	59 (35.3%)	0 (0%)	8 (44.4%)	12 (63.2%)	21 (53.8%)
2, abs (rel)	46 (27.5%)	0 (0%)	5 (27.8%)	3 (15.8%)	12 (30.8%)
3, abs (rel)	28 (16.8%)	0 (0%)	5 (27.8%)	2 (10.5%)	6 (15.4%)
≥4, abs (rel)	11 (6.6%)	0 (0%)	0 (0%)	2 (10.5%)	0 (0%)
lymphocytes count (/µl), median (IQR)	1591 (1226-2060)	2060 (1754-2447)	1690 (1321-2132.5)	1515 (1130-2097)	1421 (1136-1745)

	teriflunomide	glatiramer acetate	fingolimod	natalizumab	daclizumab
Patients, abs (rel)	11 (6.6%)	12 (7.2%)	26 (15.6%)	10 (6%)	7 (4.2%)
Age bl (years), median (IQR)	51 (38-53)	29 (24.5-36.5)	38.5 (34-46.5)	32.5 (25-49.75)	34 (27-53)
Gender f, abs (rel)	6 (45.5%)	10 (83.3%)	20 (76.9%)	7 (70%)	5 (71.4%)
Weight (kg), median (IQR)	68 (54-81)	70.5 (62.5-93.25)	74 (66-79.5)	78 (56-85)	56.5 (53.75-78)
Disease duration since diagnosis (months), median (IQR)	86.5 (21.25-246.25)	28.5 (18-94.25)	117 (70.25-168.25)	161 (41-227)	89 (46-156)
EDSS bl, median (IQR)	3 (2-3)	2 (1.375-3.250)	2 (1.5-3.125)	1.5 (0.5-2.5)	2 (0-3)
ARR at bl	1 (1-2)	1 (1-1.75)	1 (0-2)	0 (0-1)	0 (0-1)
MRI progress bl, abs (rel)	8 (72.7%)	8 (91.7%)	14 (53.8%)	3 (30%)	2 (28.6%)
number of previous DMT, median (IQR)	2 (1-3)	1 (1-2)	2 (2-3)	2 (1.75-3)	3 (2-4)
0, abs (rel)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
1, abs (rel)	5 (45.5%)	8 (66.7%)	3 (11.5%)	2 (20%)	0 (0%)
2, abs (rel)	1 (9.1%)	2 (16.7%)	16 (61.5%)	4 (40%)	3 (42.9%)
3, abs (rel)	4 (36.4%)	2 (16.7%)	4 (3.8%)	3 (30%)	1 (14.3%)
≥4, abs (rel)	1 (9.1%)	0 (0%)	3 (11.5%)	1 (10%)	3 (42.9%)
lymphocytes count (/µl), median (IQR)	1340 (1020-1512)	1846.5 (1533.75-2382.5)	1170 (1080-1361)	3142 (2330-4020)	1638 (1591-2180)

3.3 Previous DMT

Out of 167 patients, 23 (13.8%) were treatment-naive, while 144 (86.2%) had received one or more disease-modifying therapies prior to starting cladribine. Among those 167 patients, the majority had received one prior DMT (59 patients, 35.3%), followed by two prior DMTs (46 patients, 27.5%) and three prior DMTs (28 patients, 16.8%). Only a small proportion had received four or more prior DMTs (11 patients, 6.6%) (Figure 5).

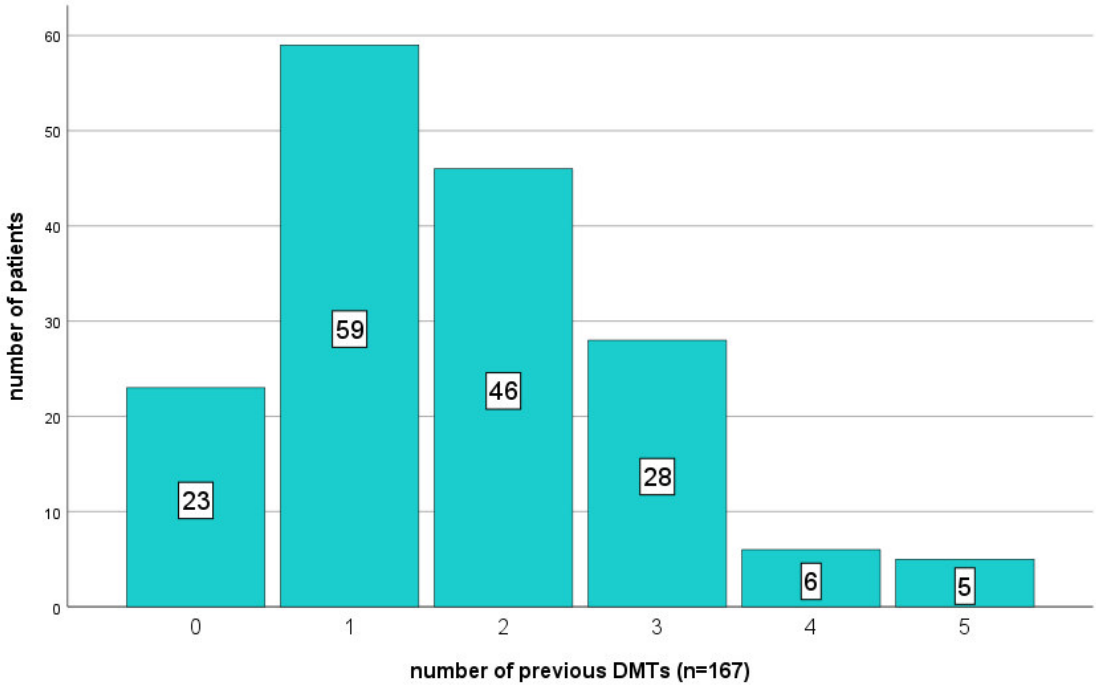


Figure 5: The number of prior disease-modifying treatments in our patient population is shown. The majority of patients had received treatment prior to cladribine, while 13.8% of patients were treatment-naive.

The analysis comprises 23 treatment-naive patients (13.8%), 18 patients who had received a DMT more than one year prior to baseline (10.8%), and 126 patients who had received a DMT less than one year prior to baseline (75.4%). Figure 6 illustrates this distribution and further stratifies the subgroups based on their previous DMT.

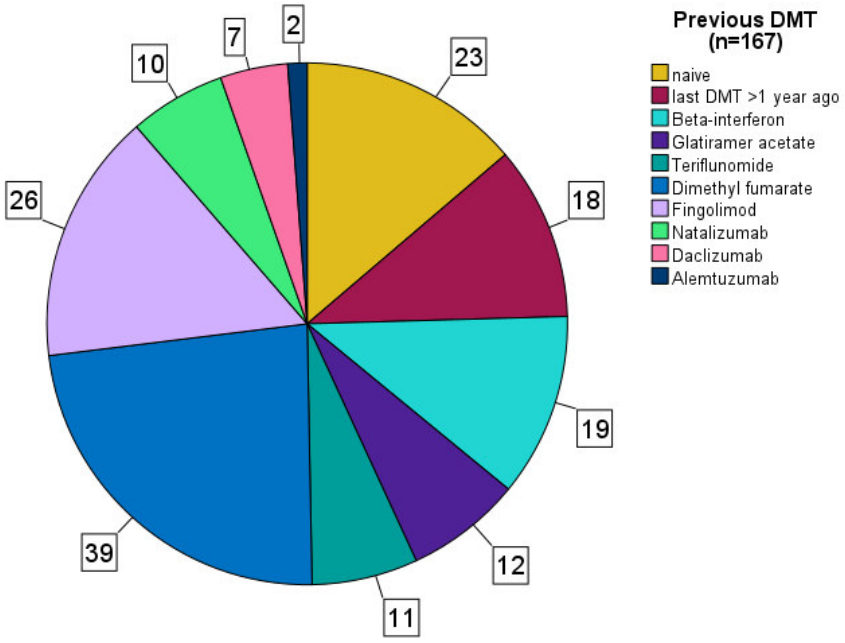


Figure 6: The proportions of the previous treatments are shown. Most patients were previously treated with dimethyl fumarate.

In the following, previous DMTs were divided into platform treatment (beta-interferon, teriflunomide, dimethyl fumarate, glatiramer acetate) and high efficacy treatment (fingolimod, natalizumab, alemtuzumab, daclizumab) (Fig. 7). The majority of patients received a platform treatment prior to cladribine (n=81, 64.3%), with dimethyl fumarate (n=39, 31%) and beta-interferon (n=19, 15.1%) being the most common agents, while a smaller proportion of patients received a high efficacy treatment prior to cladribine (35.7%), with fingolimod (20.6%) and natalizumab (8%) being the most common agents.

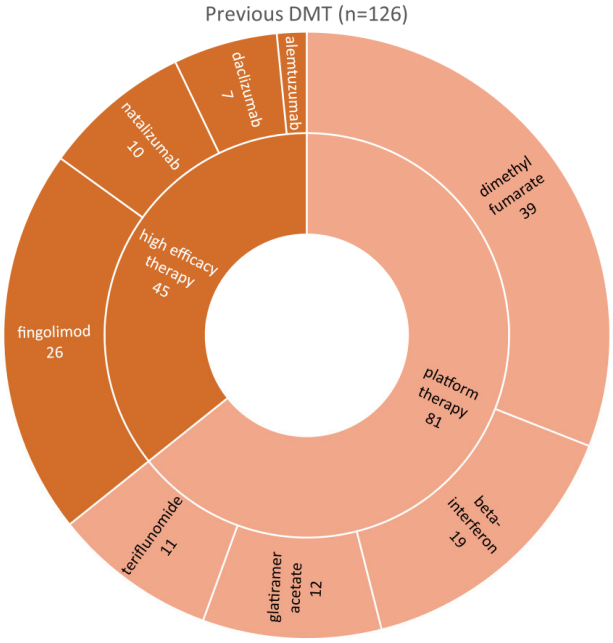


Figure 7: The proportions of previous treatments are shown, stratified by platform therapy and high efficacy therapy. Most patients were previously treated with platform therapy

3.3.1 Reasons for treatment change

There were several reasons for patients to initiate treatment with cladribine (Fig. 8). Patients who were treatment naive or who had received their last DMT more than one year prior to initiating cladribine were also included and represent a large proportion of 41 patients (24.6%). Among patients treated within one year prior to starting cladribine, the most common reasons for switching from a previous DMT to cladribine were clinical or MRI worsening, which accounted for the largest proportion of 87 patients (52%) (49 patients (29.3%) with both, 22 patients (13.2%) with clinical worsening and 16 patients (9.6%) with MRI worsening only). In addition, side effects on the previous DMT were the main reason for switching to cladribine in 27 patients (16.2%). Other reasons for switching treatment included a switch from daclizumab due to the Dear Doctor letter (4.2%) and pregnancy (1.8%).

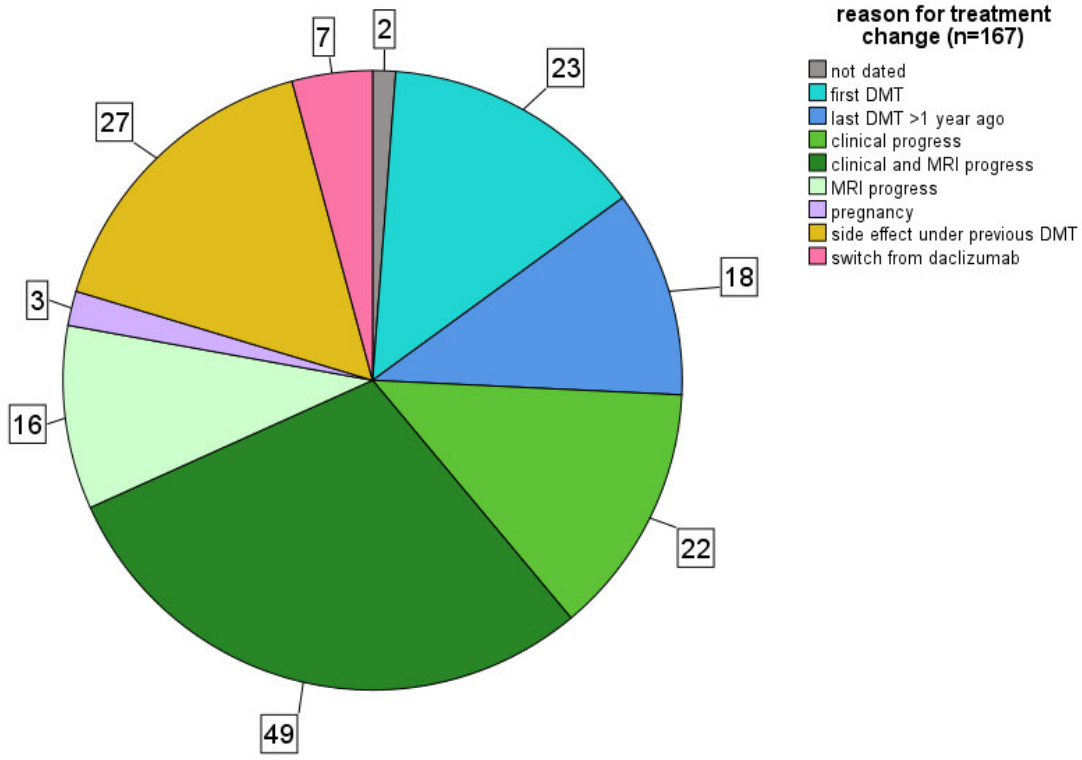


Figure 8: The reasons for changing treatment are shown. Most patients switched due to clinical or MRI progression

3.4 Clinical Efficacy

In order to assess the clinical efficacy of cladribine treatment, the three parameters annual relapse rate, MRI progression and EDSS worsening were monitored over the respective time periods as shown in Figures 9-12. MRI progression is determined by the emergence of new T2 lesions in the imaging. Furthermore, the Wilxocon test with Bonferroni correction was employed to ascertain whether there was a significant reduction in relapse rates and MRI progression between one year prior to Cladribine initiation and the treatment years 1-6.

3.4.1 Annual relapse rate

Relapses were recorded between year 2 prior to starting cladribine and year 6 of cladribine treatment. Figure 9 shows the mean relapse rate per periode (number

of relapses in one year) as determined by year of treatment, illustrating the influence of cladribine treatment on the trend in relapse rates. Two years prior to starting cladribine, the relapse rate was 0.57, while one year prior to starting cladribine, the relapse rate peaked at 1.21 relapses per year, reflecting the previously discussed finding that relapse rate is an important factor in treatment switching. After cladribine initiation, there's a steep decline in relapse rates, with an annualized relapse rate of only 0.28 in the first year, a minimum of 0.15 in the second year and 0.17 in the third year. While year 4 shows a slight increase in the relapse rate to 0.29, year 5 shows a further decrease to 0.2, with a final relapse rate of 0.11 in year 6. In conclusion, a significant reduction in the relapse rate was observed in each subsequent treatment year following cladribine induction, in comparison to the relapse rate observed in the year prior to cladribine induction.

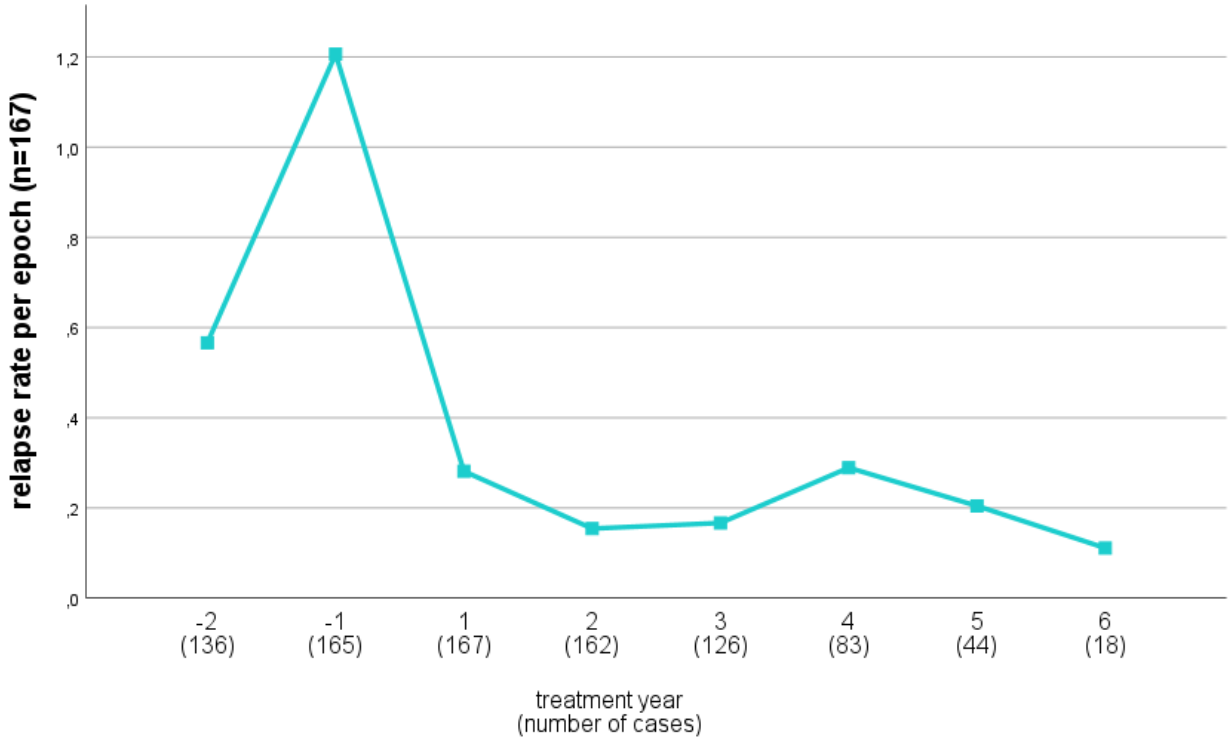


Figure 9: The annual relapse rate over the years before and during cladribine treatment is shown. There is a clear reduction in relapse rates after cladribine administration. The number of remaining patients is indicated below each year of treatment.

3.4.2 MR Imaging

The time period for recorded T2-lesions in MR imaging ranges from one year prior to the initiation of cladribine until year 5 of treatment. Figure 10 illustrates the proportion of patients with new T2-lesions depending on their treatment year and demonstrates the impact of cladribine treatment on MRI-progression. Prior to initiation of cladribine, 69% of patients showed new T2-lesions in MRI, which, along with relapse rates, indicates that MRI-progression is an important factor for switching to cladribine. Following treatment initiation, the curve declines to 31% of patients with MRI progression in year 1 and reaches a minimum of 12% with MRI progression in years 2 and 3. Similar to relapse rates, the MRI progression reveals a rise in year 4, with 21% of patients showing progression. However, this progression again declines in year 5, with only 19% of patients experiencing MRI progression. As with relapse rates, each subsequent treatment year following cladribine induction demonstrated a significantly lower MRI progression rate than the year prior to cladribine induction.

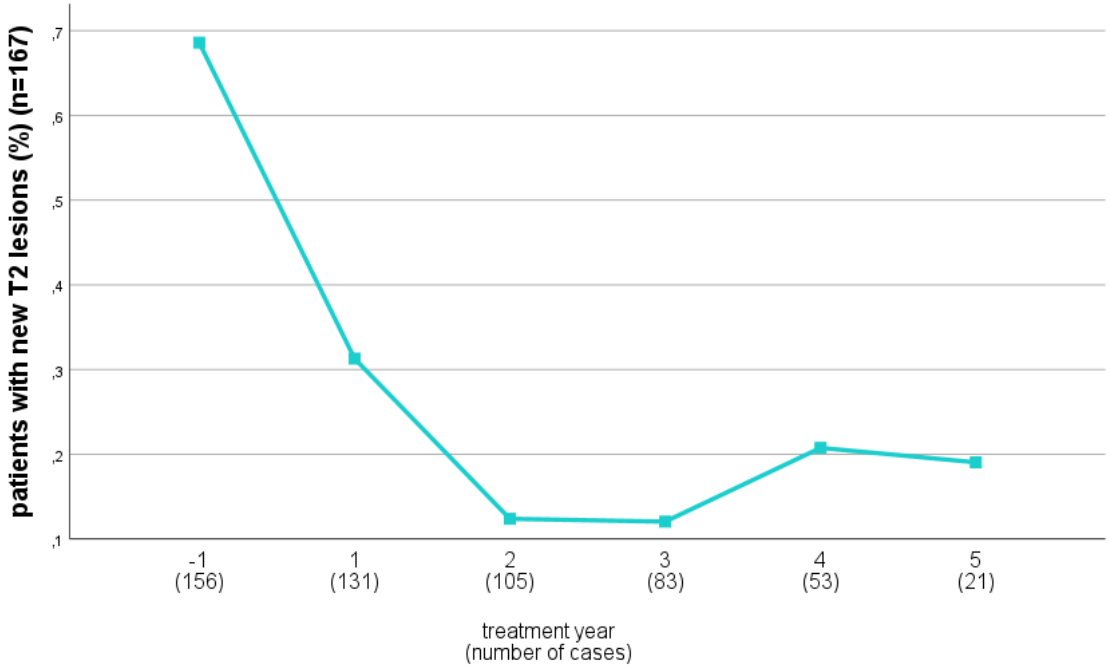


Figure 10: MRI progression over the years before and during cladribine treatment is shown. There is a clear reduction in MRI progression after cladribine administration. The number of remaining patients is indicated below each year of treatment.

3.4.3 EDSS

The Expanded Disability Status Scale (EDSS) was recorded from baseline to year 5 of cladribine treatment and is depicted in Figures 11 and 12.
Figure 11 shows a box-and-whisker plot of the median EDSS per year, starting with a median EDSS of 2 at baseline (IQR=1-3). The median EDSS of 2 remains stable in the first 3 years with a slight variation of 0.25 and 0.75 percentiles. At year 4, the median rises to 2.5 and remains at this value until year 5.

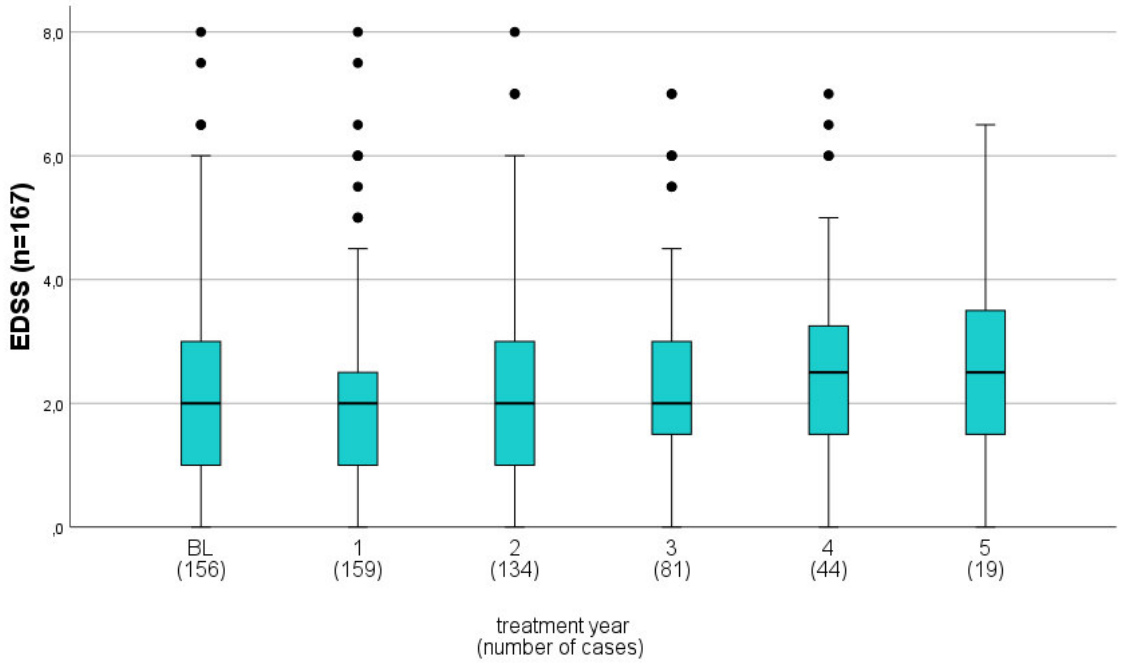


Figure 11: EDSS progression over the years with cladribine treatment is shown. The EDSS course remains almost stable, although a small increase can be seen. The number of remaining patients is indicated below each year of treatment.

To demonstrate the impact of cladribine on EDSS, the delta EDSS was calculated for each year of treatment as the difference between the EDSS score in that year and the previous year and its mean value plotted on a bar chart (Fig. 12). The first year of cladribine treatment resulted in a mean reduction of EDSS of 0.08. However, in the following years, there was a slight increase in EDSS, starting from 0.019 in year 2, increasing to 0.84 in year 3, and peaking at 0.098 in year 4. There was no change in mean EDSS observed in year 5, which may reflect the limited number of patients and drop outs in that year.

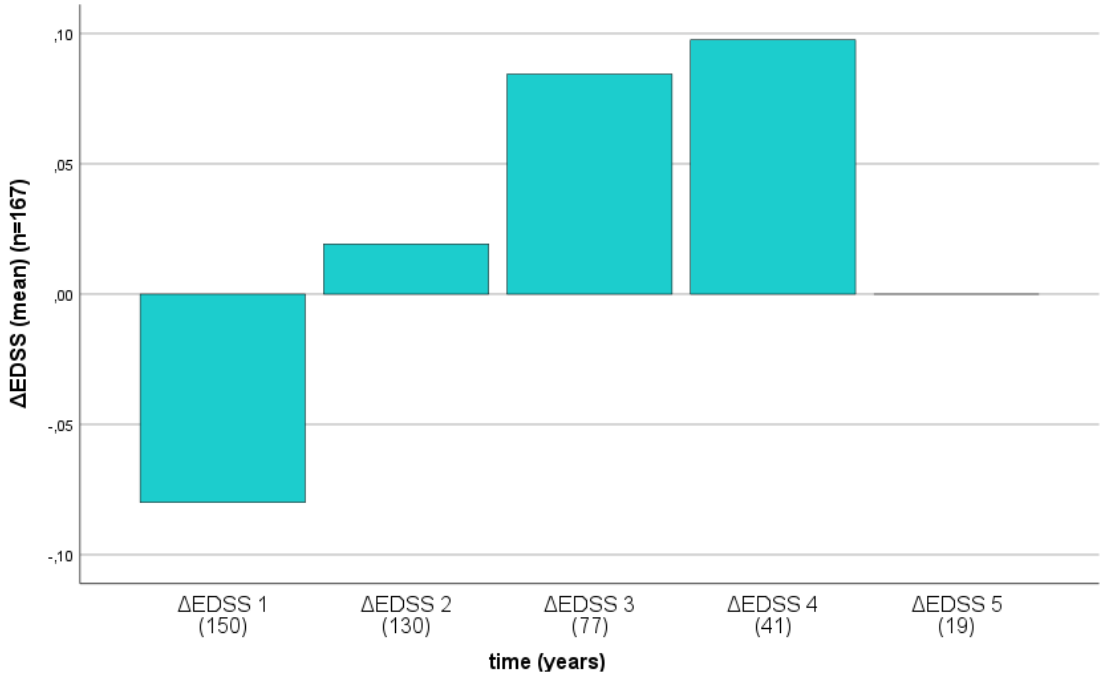


Figure 12: The delta EDSS over the years with cladribine treatment is shown. The greatest decrease in EDSS was seen in year 1, while the greatest increase in EDSS was seen in year 4. The number of remaining patients is indicated below each year of treatment.

3.5 Adverse events

A total of 64 patients reported 91 adverse events after undergoing the first or second treatment cycle. To provide a clearer overview, adverse events were classified into several groups. The 'general conditions' group included headache, fatigue, nausea, and circulation problems. The 'infections' group included herpes zoster infection, oral herpes infection, and other infections. The 'skin & skin appendage' group included alopecia, exanthema, pruritus, and other related conditions, which made up a small proportion. The most frequent adverse event reported was headache (24%), followed by fatigue (19%), herpes zoster infection (13%), nausea and alopecia (9% each), and exanthema (8%). Adverse events with a lower incidence included oral herpes (4%), circulation problems (4%), other infections (3%), and pruritus (2%). Moreover, no severe adverse events were reported. (Fig. 13)

Figure 13: The adverse events associated with cladribine treatment are shown. The most common adverse events were headache and fatigue.

3.6 Laboratory Values

3.6.1 Lymphocyte counts

Lymphocyte counts were recorded at the start of each treatment cycle and again after 4 to 8 weeks, with follow-up every 3 months. The data are presented in the form of a boxplot diagram (Fig. 14). Patients entered the study with a median lymphocyte count of 1465.5 lymphocytes/µl at baseline, which decreased rapidly to a median of 800 lymphocytes/µl at 4-8 weeks after baseline. The count remained almost stable at month 3. At month 6, there was a slight increase in the median lymphocyte count to 940 lymphocytes/µl, which maintained an almost stable level in month 9 and rose to 1036 lymphocytes/µl at month 12. This count serves as the baseline for the second treatment cycle and is 429.5 lymphocytes/µl lower than the median baseline count of the first treatment cycle. The second cycle is followed by an absolute minimum of 570 lymphocytes/µl 4-8 weeks after the second baseline, which remained almost stable at 592 lymphocytes/µl in month 3 after the second baseline and then began to recover to 750 lymphocytes/µl in month 6 after the second baseline. The lymphocyte count continued to rise gradually until week 33 (21 weeks after the second baseline),

when it reached a median of 1283.5 lymphocytes/µl. For the next 9 months, the lymphocyte count fluctuated below this level. However, in month 45, the count peaked at 1492 lymphocytes/µl. In the last month recorded, the lymphocyte count showed a slight decrease to 1278 lymphocytes/µl.

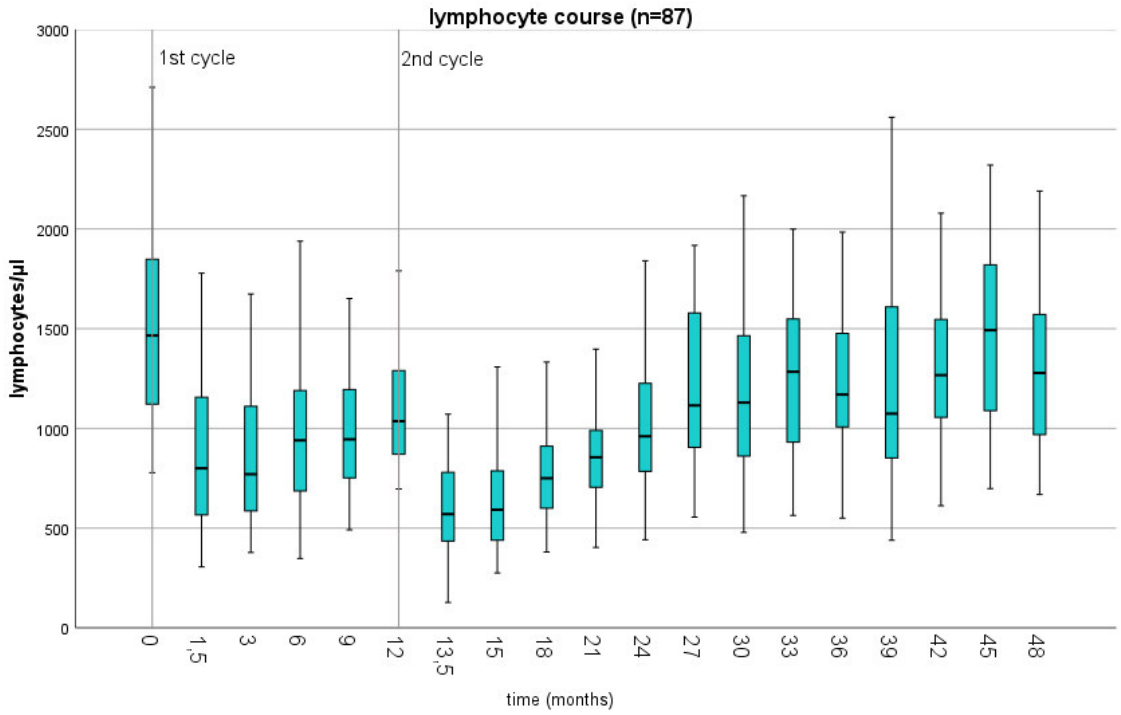


Figure 14: The course of the lymphocyte count during cladribine treatment is shown. There is a clear decrease in the lymphocyte count after the first and second cladribine cycles.

In addition, 1.5 to 3 months after the first and second cycles, the lowest lymphocyte count of each patient was categorised into lymphopenia grades (Fig 15). Grade 4 includes lymphocyte counts of less than 200 lymphocytes/µl, while grade 3 includes lymphocyte counts of 200-500 lymphocytes/µl, grade 2 includes lymphocyte counts of 500-800 lymphocytes/µl, and grade 1 includes lymphocyte counts of 800-1000 lymphocytes/µl. Grade 0, which refers to no evidence of lymphopenia, includes all lymphocyte counts above 1000 lymphocytes/µl. Figure 15 displays the percentage of lymphopenia grades following the first and second cycle of cladribine treatment. After the initial cycle, 21.26% of patients did not experience lymphopenia, while 15.75% of patients had a lymphopenia grade 1. Notably, the majority of patients, 48.82%, developed lymphopenia grade 2 and

14.17% of patients developed lymphopenia grade 3. No patients experienced grade 4 lymphopenia during the first treatment cycle. In the second treatment cycle, there was a slight shift in the distribution of lymphopenia grades. Here, only 10.24% of patients were spared from lymphopenia. Additionally, the lymphopenia grade 1 and 2 patient populations exhibited reduced patient numbers. Of the total cohort, 9.45% exhibited grade 1 lymphopenia, while 44.88% demonstrated grade 2 lymphopenia. However, the percentage of patients with grade 3 lymphopenia increased to 33.86%, and two patients (1.57%) even suffered from grade 4 lymphopenia.

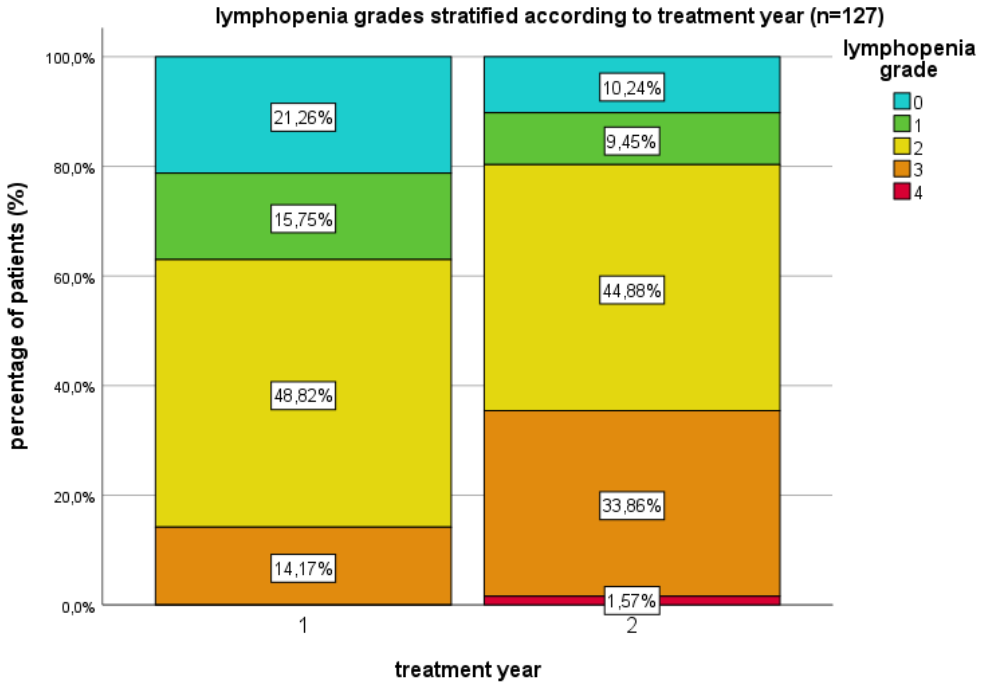


Figure 15: Lymphopenia grades in the first and second year of treatment with cladribine are shown. Most patients experienced grade 2 lymphopenia.

3.7 Treatment switch

During the observation period of the analysis, 18 out of 167 patients (10.78%) switched to another disease-modifying treatment due to the reasons discussed below.

3.7.1 Year of treatment switch

Figure 16 depicts the year of treatment switches, which ranged from year two to year five. In year two, only 2 patients (11.1%) switched treatments, while in year three, 3 patients (16.7%) changed treatments. The highest number of treatment switches occurred in year four, with 7 patients (38.9%) switching from cladribine to another DMT. Year five showed a total of 4 patients (22.2%) switching to another treatment. For 2 patients (11.1%), the year of treatment change was not dated.

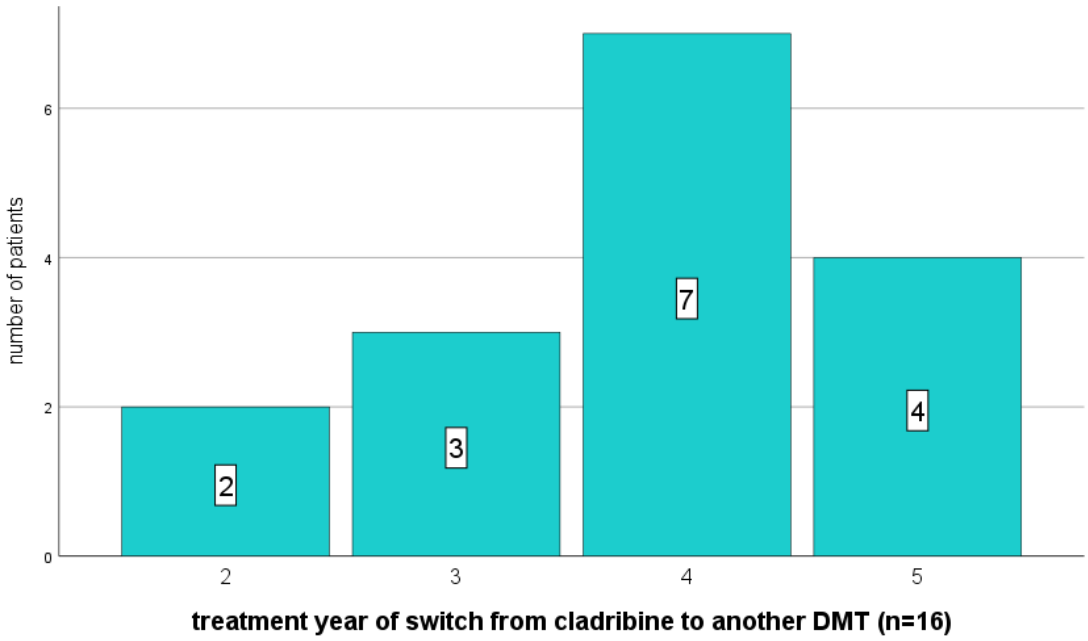


Figure 16: The year of treatment switch from cladribine to another DMT is shown. Most patients switched in the fourth year of treatment.

3.7.2 Reason for treatment switch

The main reason for switching from cladribine to another disease-modifying treatment (Fig. 17) was a combination of clinical and MRI progress, which was evident in 13 out of 18 patients (72.2%). A smaller proportion of patients, 3 out of 18 (16.7%), switched due to isolated clinical progress. The reason for treatment switch was not available for 2 out of 18 patients (11.1%).

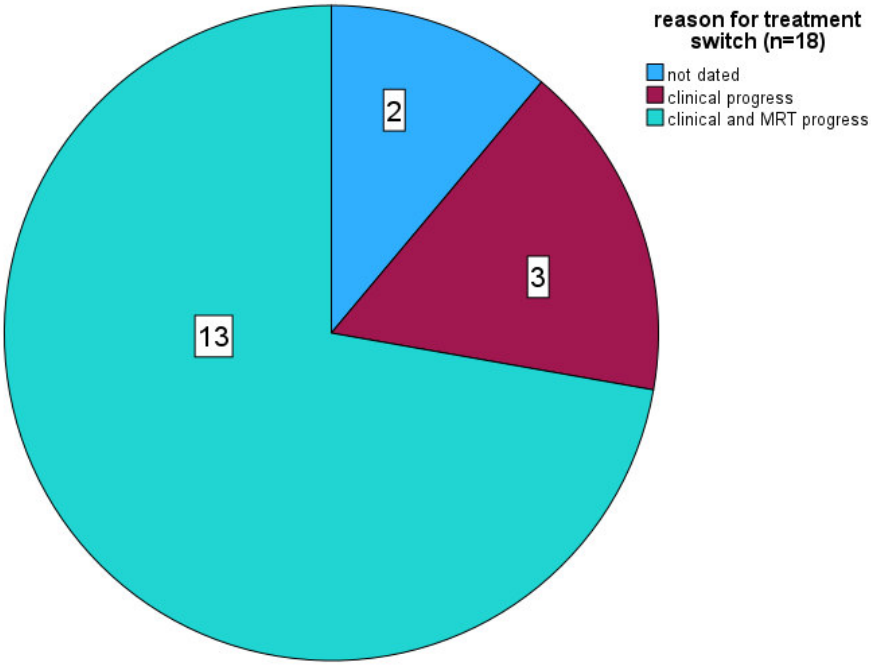


Figure 17: The reasons for switching from cladribine to another DMT are shown. All patients switched treatment due to either clinical or MRI activity.

3.7.3 Following DMT

In total, 4 different disease-modifying therapies were started after the decision to switch treatment (Fig 18). While 1 patient (5.6%) started treatment with natalizumab, another patient (5.6%) started treatment with siponimod. In addition, a larger proportion of 4 patients (22.2%) were treated with ofatumumab. Notably, the largest percentage of 12 patients (66.7%) switched to treatment with ocrelizumab.

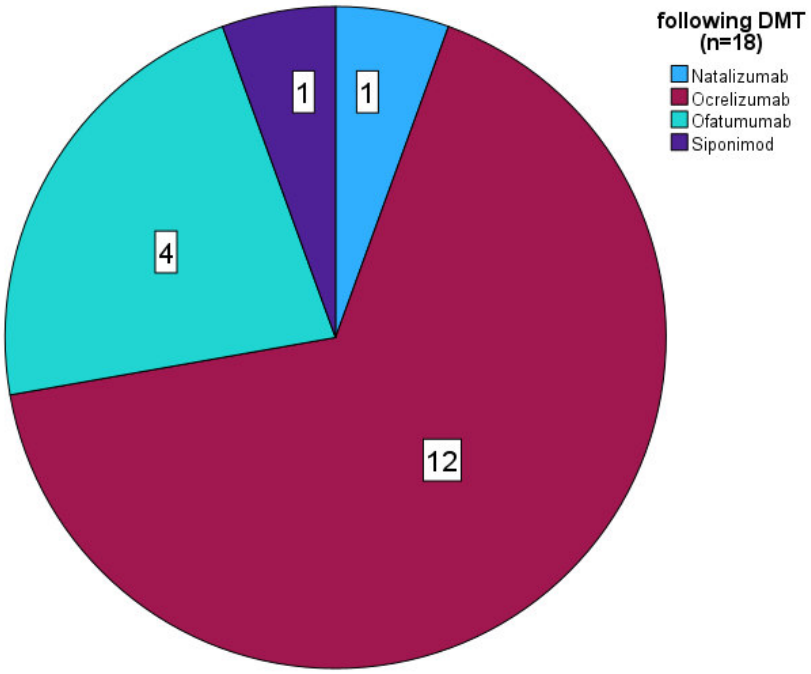


Figure 18: The following DMTs are shown after switching from cladribine. Most patients switched to ocrelizuab

3.8 Effect of previous DMT on the efficacy of cladribine treatment

To investigate the impact of previous disease-modifying treatment on the efficacy of cladribine treatment, patients were stratified according to their previous DMT and the respective efficacy parameters relapse rate, T2 lesions on MRI and EDSS progression were plotted on a Kaplan-Meier curve. The number of patients remaining is indicated below each diagram. Median and mean values of the survival time are given for each graph (Table 2-6).

3.8.1 Clinical relapses

Clinical relapses are shown over a period of 5 years from baseline. Figure 19 displays the percentage of patients who remained free of clinical relapses during this time period, stratified by their previous disease-modifying therapy, including platform treatment, fingolimod, natalizumab, as well as treatment-naive patients. At the outset, patients who had previously received fingolimod as a DMT appear to perform the worst, with only 57.7% of patients remaining relapse-free in year 1. There was a slight decrease in the number of relapse-free patients in the

second year to 50%. However, the rate of relapse-free patients remained stable over the next three years until year five, when the proportion of relapse-free patients reached 45%. Patients who were naive to treatment and those who had received previous platform treatment showed better outcomes initially. In the first year, 78.3% of naive patients remained relapse-free, while 82.5% of patients who had previously received a platform treatment didn't experience a clinical relapse in the same year. Subsequently, the rate of relapse-free patients decreased gradually in both groups. In the final evaluation, 36.5% of naive patients remained relapse-free until year 4. Following this point, no naive patients were left for further evaluation. For patients who had received previous platform treatment, the probability of remaining relapse-free was 57.2% until year 4 and 52% until year 5. A clinical relapse was not observed in patients previously treated with natalizumab during the first years of follow-up, resulting in a 100% relapse-free rate until year 2. The first decline occured in year 3, resulting in a relapse-free rate of 85.7% that continues into year 4. However, the subsequent year demonstrated a further decline, resulting in a proportion of 57.1% of patients being relapse-free at the conclusion of the evaluation.

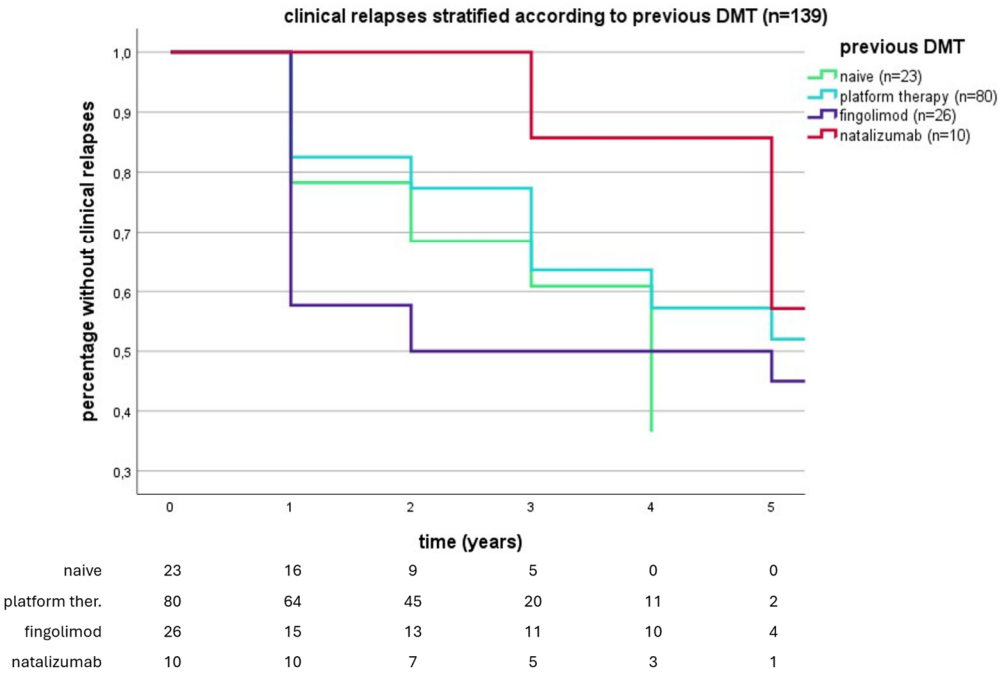


Figure 19: The Kaplan-Meier curve shows the percentage of patients without clinical relapse stratified by previous treatment over time. The remaining patients are shown in the table below. While natalizumab patients showed the best outcome, fingolimod patients showed a rather poor course, with naive and platform patients in between.

Table 2: Mean and median time to first clinical relapse, stratified by previous treatment

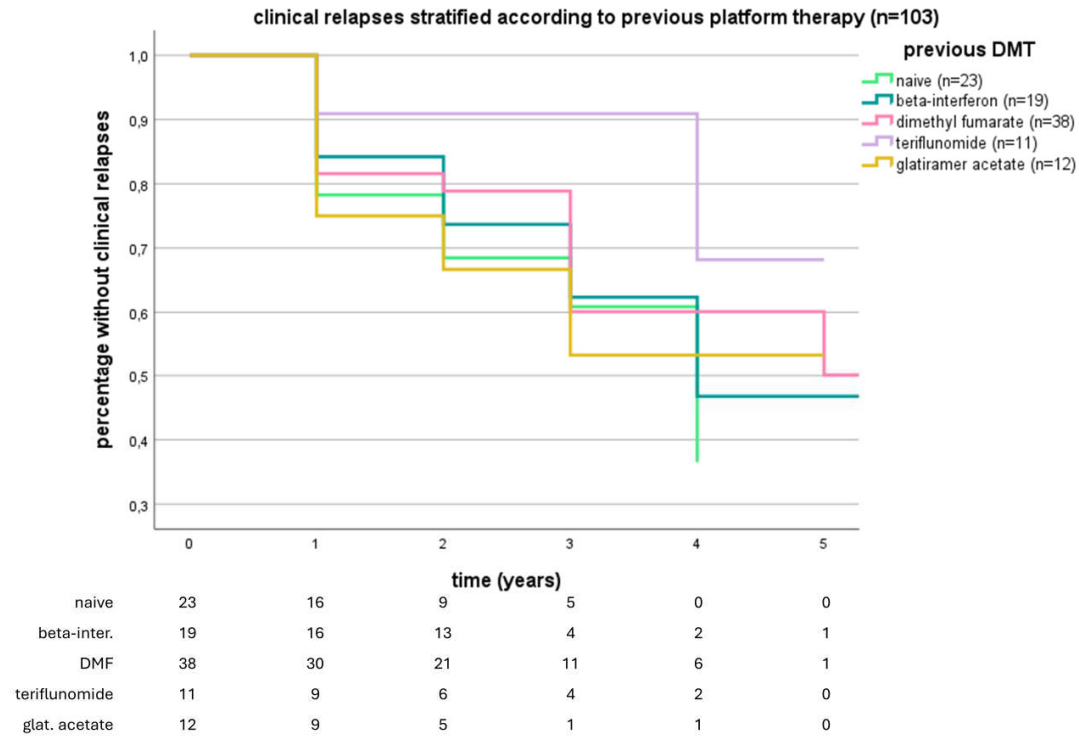
Previous treatment	Mean	Standard error	95% confidence interval	Median	Standard error	95% confidence interval
Naive	3.076	0.283	2.521-3.631	4.000	0.615	2.794-5.206
Platform therapy	4.327	0.244	3.850-4.804	x	x	x
Fingolimod	3.527	0.470	2.605-4.449	2.000	3.090	0.000-8.057
Natalizumab	5.286	0.423	4.457-6.115	x	x	x

To account for the great variety in courses among patients with previous platform treatments, patients were further stratified into groups according to their previous platform treatment, which included beta-interferon, dimethyl fumarate, teriflunomide and glatiramer acetate. Naive patients were also included for comparison (Fig 20).

In the first year of Cladribine induction, different platform therapies showed varying proportions of relapse-free patients. Teriflunomide represented the best subgroup with 90.9% of patients remaining relapse-free, followed by beta-interferon with 84.2%, dimethyl-fumarate with 81.6%, and finally glatiramer

acetate with only 75% of patients remaining relapse-free in year 1. For comparison, 78.3% of treatment-naive patients remained relapse-free in year 1. Thereafter, the relapse-free rate gradually decreased in all subgroups except teriflunomide, which remained stable at 90.9% until year 3, before decreasing to a rate of 68.2% relapse-free patients in year 4 and 5.

Meanwhile, other platform therapies exhibited poorer outcomes, with beta-interferon demonstrating a relapse-free rate of only 46.8%, dimethyl-fumarate with a rate of 50.1%, and glatiramer acetate with a proportion of 53.3% in year 5.



naive	23	16	9	5	0	0
beta-inter.	19	16	13	4	2	1
DMF	38	30	21	11	6	1
teriflunomide	11	9	6	4	2	0
glat. acetate	12	9	5	1	1	0

Figure 20: The Kaplan-Meier curve shows the percentage of patients without clinical relapse stratified by prior platform treatment over time. The remaining patients are shown in the table below. While all platform treatments showed a fairly similar course, patients treated with teriflunomide showed the best outcome.

Table 3: Mean and median time to first clinical relapse, stratified by previous platform treatment

Previous treatment	Mean	Standard error	95% confidence interval	Median	Standard error	95% confidence interval
Naive	3.076	0.283	2.521-3.631	4.000	0.615	2.794-5.206
Beta-interferon	4.138	0.501	3.156-5.120	4.000	x	X
Dimethyl fumarate	4.307	0.352	3.618-4.996	X	x	x
Teriflunomide	4.409	0.380	3.664-5.154	x	x	X
Glatiramer acetate	3.483	0.520	2.465-4.502	x	x	x

3.8.2 MRI progress

T2 lesions were recorded on MR imaging over a 5-year period from the onset of cladribine. Figure 21 shows the proportion of patients who did not experience MRI progression over time, stratified according to their previous disease-modifying therapy (DMT), including platform treatment, fingolimod, natalizumab, as well as treatment-naive patients.

In the first year, patients who were naive as well as those treated with fingolimod and a platform treatment showed MRI progression. Among them, naive patients had the worst start, with only 65% of patients showing no clinical progress. Patients treated with platform treatment showed a slightly better course in the first year with a rate of 73.7% progress-free patients, while fingolimod-treated patients showed a rate of 75% progress-free patients.

In contrast, the rate of relapse-free patients for those treated with natalizumab remained at 100% in year 1.

The progression course of naive patients continued as it began. The proportion of progression-free patients gradually decreased to 47.3% in year 2 and 35.5% in year 3, where it remained until year 4, which marks the conclusion of the evaluation for naive patients.

A better progression course is depicted by patients treated with platform treatment and fingolimod: while the progression-free rate in year 2 was 68.9% for platform-treatment and 70.8% for fingolimod, the progression rate in year 3 was 60% for platform-treatment and 66.4% for fingolimod and the progression rate in year 4 was 55.4% for platform-treatment and 59% for fingolimod, where it remained until year 5.

Patients treated with natalizumab, who initially responded well to cladribine initiation, exhibited a steep decrease in year 2 to a progression-free rate of 71.4%. However, there was a period of stagnation until year 3, after which the rate declined to 35.7% in year 4 and maintained a steady level until year 5.

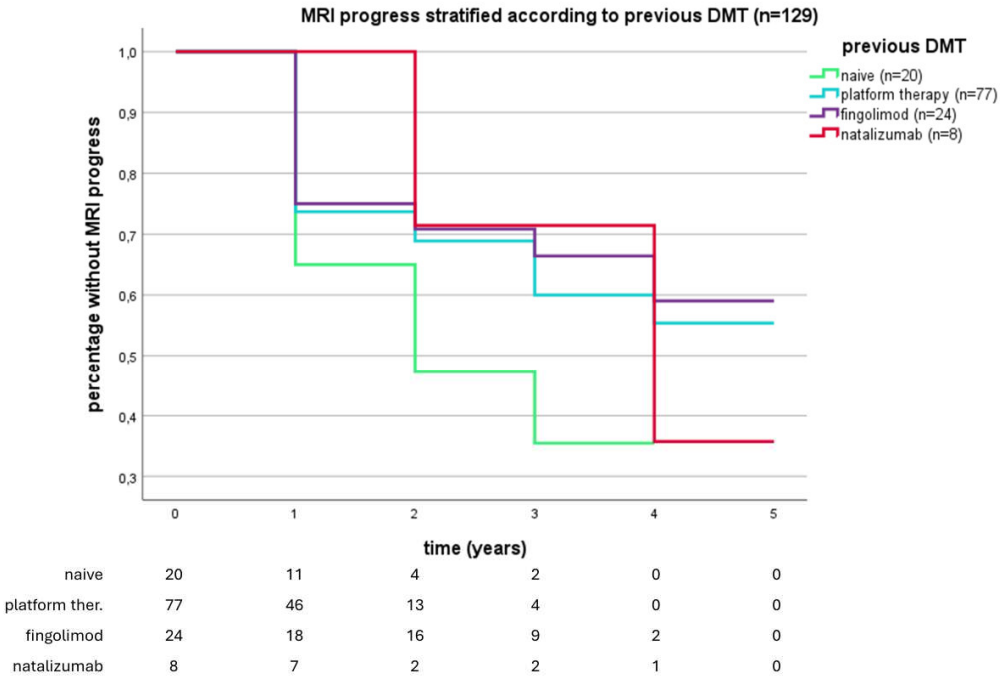


Figure 21: The Kaplan-Meier curve shows the percentage of patients without MRI progression stratified by previous treatment over time. The remaining patients are shown in the table below. While natalizumab and naive patients exhibited the worst outcome, fingolimod pre-treated patients showed the best outcome.

Table 4: Mean and median time to first MRI progress, stratified by previous treatment

Previous treatment	Mean	Standard error	95% confidence interval	Median	Standard error	95% confidence interval
Naive	2.477	0.304	1.881-3.074	2.000	0.790	0.451-3.549
Platform therapy	3.579	0.212	3.165-3.994	x	x	x
Fingolimod	3.713	0.355	3.016-4.409	x	x	x
Natalizumab	3.786	0.496	2.814-4.758	4.000	1.493	1.074-6.926

Due to the clear differences in progression courses between the various platform therapies, patients who received platform treatment were stratified based on their agent and compared to treatment-naive patients.

In the first year, relapse-free patients decreased significantly for all platform therapies. However, there was a wide range of rates. Dimethyl fumarate patients had the lowest rate in year 1, with only 65.8% of patients being progression-free. On the other hand, patients treated with glatiramer acetate showed a markedly better rate of 72.7%, followed by teriflunomide patients with a rate of 77.8% of patients without progression. Beta-interferon patients showed the best progression-free rate at 88.9%, compared to naive patients who had a rate of

only 65.0%.

Subsequently, during the following treatment period, the courses of the various platform therapies exhibited significant variation.

The proportion of dimethyl fumarate treated patients who remained progression-free continued to decline in a stepwise manner, starting at 59.8% in year 2 and ultimately reaching a rate of 41.1% in year 5.

A better course was demonstrated by glatiramer acetate, which halted disease progression at a rate of 72.7% until year 2 and then decreased to 48.5% in year 3, finally leading to the end of the disease course.

In contrast, the progress of teriflunomide remained at 77.8% until year 5.

The treatment option with the highest rate of progression-free patients was beta interferon, which demonstrated a slight decrease in year 2 to 83.0%, but maintained this level until year 5.

In comparison, the progression-free rate of naive patients was only 35.5% in year 4.

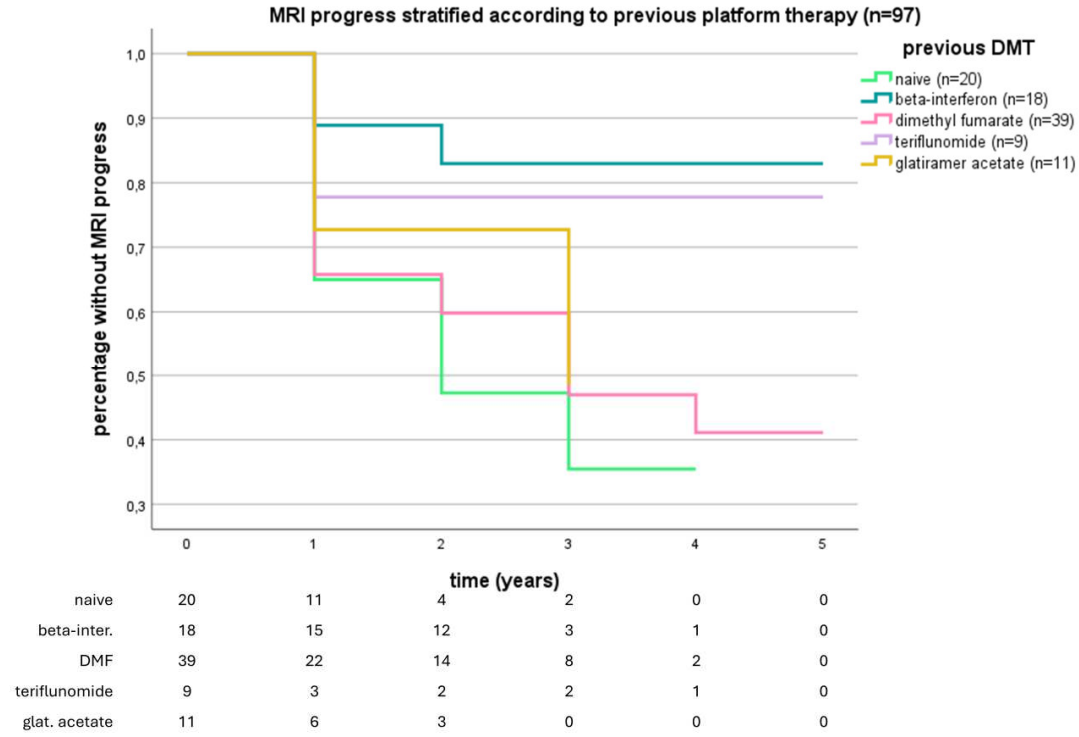


Figure 22: The Kaplan-Meier curve shows the percentage of patients without MRI progression stratified by previous platform treatment over time. The remaining patients are shown in the table below. While beta-interferon patients showed the best outcome, naive patients and dimethyl fumarate pre-treated patients showed the worst outcome.

Table 5: Mean and median time to first MRI progress, stratified by previous platform treatment

Previous treatment	Mean	Standard error	95% confidence interval	Median	Standard error	95% confidence interval
Naive	2.477	0.304	1.881-3.074	2.000	0.790	0.451-3.549
Beta-interferon	4.378	0.330	3.731-5.024	x	x	X
Dimethyl fumarate	3.137	0.301	2.547-3.727	3.000	0.977	1.086-4.914
Teriflunomide	4.111	0.554	3.025-5.198	x	x	x
Glatiramer acetate	2.455	0.310	1.847-3.062	3.000	x	x

3.8.3 EDSS

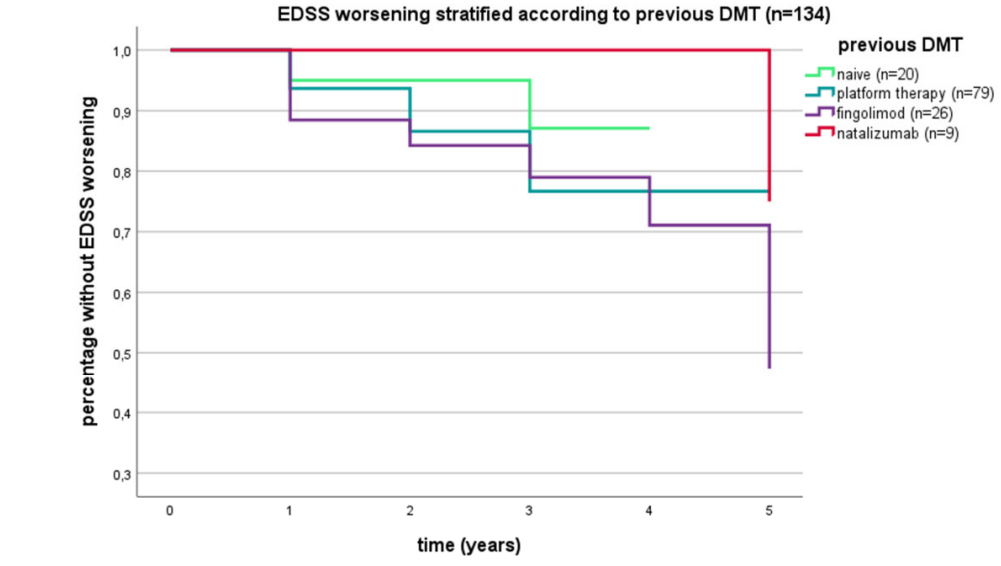
EDSS values were recorded over a 5-year period from onset. Figure 23 shows the proportion of patients whose EDSS did not worsen over time, stratified according to the previous disease-modifying therapy, including platform treatment, fingolimod, and natalizumab. Unlike the relapse course and MRI progression course, there was no significant variation in the courses of the

different platform therapies. Therefore, platform therapies were not presented in a separate figure for EDSS course.

Starting in year 1, there was only a slight decrease in the number of patients with EDSS worsening in this treatment year. The lowest rate of worsening-free patients was observed with fingolimod at 88.5%, followed by platform treatment at 93.7%, and natalizumab, which maintained a rate of 100%. In comparison, treatment-naive patients exhibited a worsening-free rate of 95%.

Over time, the courses of platform-treatment and fingolimod remained fairly similar: In year 2, fingolimod showed a worsening-free rate of 84.2% and platform treatment a rate of 86.6%; in year 3, the rate was 79% for fingolimod and 76.7% for platform treatment; and in year 4, fingolimod showed a rate of 71.1% and platform treatment a rate of 76.7%. While platform treatment maintained a stable rate at year 5, fingolimod exhibited a marked decrease to 47.4%.

In contrast, natalizumab showed an almost stable course, maintaining a rate of 100% of patients free from worsening until year 4, after which it fell sharply to 75% in year 5.



naive	20	18	12	3	0	0
platform ther.	79	66	35	17	9	0
fingolimod	26	21	16	10	6	0
natalizumab	9	7	5	5	4	0

Figure 23: The Kaplan-Meier curve shows the percentage of patients without EDSS worsening stratified by previous treatment over time. The remaining patients are shown in the table below. While platform treatment and natalizumab patients fared best, fingolimod patients fared worst

Table 6: Mean and median time to first EDSS worsening, stratified by previous treatment

Previous treatment	Mean	Standard error	95% confidence interval	Median	Standard error	95% confidence interval
Naive	3.771	0.161	3.455-4.087	x	x	X
Platform therapy	4.336	0.159	4.024-4.648	X	x	x
Fingolimod	4.228	0.303	3.634-4.822	5.000	x	X
Natalizumab	5.000	0.000	5.000-5.000	x	x	x

3.8.4 Log-Rank test

In order to ascertain whether there are significant differences in the outcome of the cladribine course depending on the previous DMT, a log-rank test was performed for each category (Table 7). However, none of the tests demonstrated a significantly different influence on the cladribine outcome course between the previous DMTs.

Table 7: Log-rank test for relapse rate, MRI progression and EDSS worsening

Log-rank test	Chi-Square	Significance
Relapse rate Stratified according to previous DMT	3.875	0.275
Relapse rate Stratified according to previous platform therapy	2.858	0.582
MRI Stratified according to previous DMT	3.445	0.328
MRI Stratified according to previous platform therapy	8.387	0.078
EDSS Stratified according to previous DMT	2.526	0.471

3.9 Effect of previous DMTs on lymphocyte count

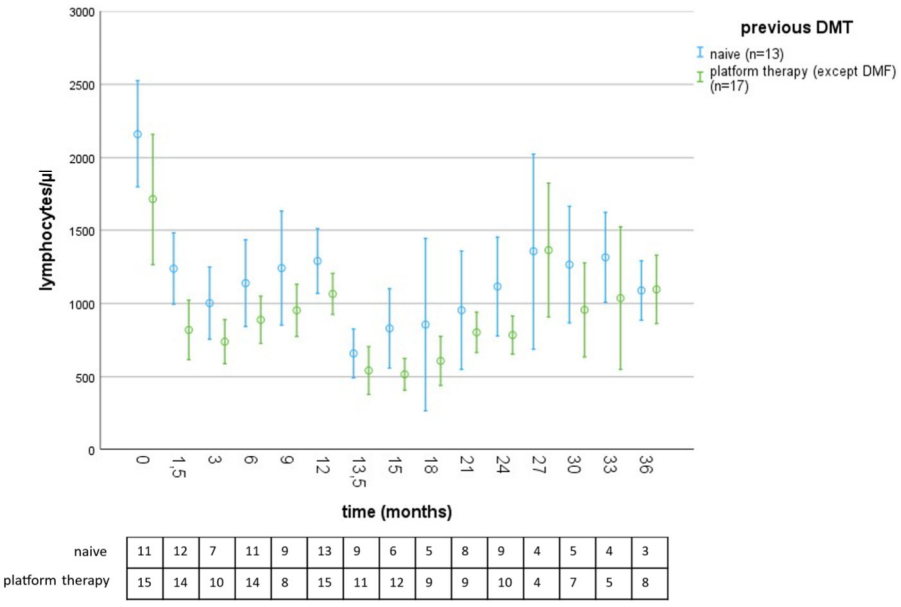
In order to evaluate the impact of previous DMTs on lymphocyte counts, patients were divided into groups according to the previous DMT. As the lymphocyte course of patients previously treated with dimethyl fumarate markedly differed from that of patients treated with another platform treatment, those groups were regarded separately. Finally, five groups were formed: naive patients, those previously treated with platform therapy (except DMF), those previously treated

with DMF, those previously treated with fingolimod and those previously treated with natalizumab. The mean lymphocyte counts of patients previously treated with platform therapy, DMF and fingolimod over a three-year period are shown in separate graphs and compared with those of naive patients. Given the lack of data available on patients previously treated with natalizumab, there is no corresponding diagram for this group of patients.

3.9.1 Platform therapy (except DMF)

Figure 24 displays the lymphocyte counts of patients who have undergone platform therapy compared to those patients who were naive to treatment. At baseline, there is a marked difference between the lymphocyte counts of the two groups. Naive patients had a baseline lymphocyte count of 2160 lymphocytes/µl, while platform treatment patients had a count of only 1712 lymphocytes/µl. After 1.5 months of treatment initiation, naive patients still had a count of 1238 lymphocytes/µl, whereas the count of platform treatment patients showed a clear decrease to 820 lymphocytes/µl. In the third month, both the naive patients and those treated with platform therapy reached a minimum in the first year, with 1003 lymphocytes/µl for the former and 740 lymphocytes/µl for the latter. In the following months, the lymphocyte counts of both groups began to slowly recover, naive patients reaching a count of 1290 lymphocytes/µl by month 12, while platform treatment patients had a lymphocyte count of 1066 lymphocytes/µl. In month 13.5, which is 1.5 months after initiation of the second treatment cycle, both patient groups experienced a marked decrease in lymphocyte counts. Naive patients exhibited a count of 660 lymphocytes/µl, which is the absolute minimum count for this group, while platform therapy patients exhibited a count of 543 lymphocytes/µl. In month 15, while patients who have not received prior treatment have already recovered to a count of 830 lymphocytes/µl, patients who have received platform treatment suffered from an absolute minimum count of 517 lymphocytes/µl. However, in the subsequent months, both groups recovered to gradually increasing lymphocyte counts, resulting in a lymphocyte count at month 24 of 1116 lymphocytes/µl for naive patients and 785 lymphocytes/µl for platform

therapy patients. The maximum for both groups was reached at month 27, when naive patients had a count of 1357 lymphocytes/µl and platform therapy patients had a count of 1364 lymphocytes/µl. Afterwards, both groups exhibited a fluctuating course. Naive patients showed a count of 1089 lymphocytes/µl and platform therapy patients of 1096 lymphocytes/µl at year 3.



naive	11	12	7	11	9	13	9	6	5	8	9	4	5	4	3
platform therapy	15	14	10	14	8	15	11	12	9	9	10	4	7	5	8

Figure 24: The graph shows a comparison between the lymphocyte counts of naive patients and patients pre-treated with a platform treatment. The remaining patients are shown in the table below. Patients with prior platform treatment showed markedly lower lymphocyte counts than naive patients throughout the observation period.

3.9.2 Dimethyl fumarate (DMF)

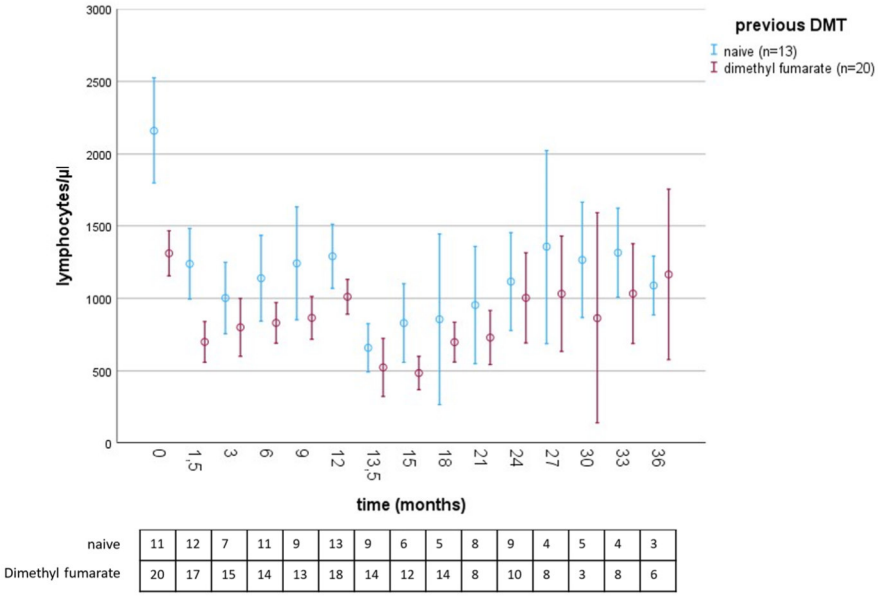
Figure 25 presents a separate representation of the lymphocyte course of dimethyl fumarate.

A clear disparity between the two groups was evident already at baseline. Naive patients exhibited a lymphocyte count of 2160 lymphocytes/µl, while patients previously treated with dimethyl fumarate exhibited a lymphocyte count of only 1311 lymphocytes/µl.

One and a half months following the initial treatment administration, patients in the dimethyl fumarate group demonstrated a minimum lymphocyte count of 700

lymphocytes/µl, while naive patients exhibited a lymphocyte count of 1238 lymphocytes/µl. In the subsequent months, patients who were previously naive to treatment demonstrated markedly accelerated recovery compared to those who had previously undergone treatment with dimethyl fumarate. This was evidenced by a lymphocyte count of 1290 lymphocytes/µl for the former group and 1011 lymphocytes/µl for the latter at month 12.

Following the second treatment application, naive patients exhibited an absolute minimum in month 13.5 with 660 lymphocytes/µl whereas patients in the dimethyl fumarate group exhibited an absolute minimum in month 15 with only 486 lymphocytes/µl. The counts gradually increased, reaching 1116 lymphocytes/µl for naive patients and 1004 lymphocytes/µl for patients previously treated with dimethyl fumarate in month 24, and 1089 lymphocytes/µl for naive patients and 1165 lymphocytes/µl for patients previously treated with dimethyl fumarate in month 36. Nevertheless, the higher lymphocyte count observed in dimethyl fumarate patients in month 36 should be interpreted with caution, given the limited number of patients involved.



naive	11	12	7	11	9	13	9	6	5	8	9	4	5	4	3
Dimethyl fumarate	20	17	15	14	13	18	14	12	14	8	10	8	3	8	6

Figure 25: The graph shows a comparison between the lymphocyte counts of naive patients and dimethyl fumarate pre-treated patients. The remaining patients are shown in the table below. Patients treated with dimethyl fumarate showed markedly lower lymphocyte counts than naive patients throughout the observation period.

3.9.3 Fingolimod

Figure 26 shows the lymphocyte counts of patients who were previously treated with fingolimod compared to those who were naive to treatment. As before, the lymphocyte count of naive patients was higher at baseline than that of patients previously treated with a DMT, in this case fingolimod. In contrast to patients who had received a platform treatment, those who had received fingolimod started with an even lower lymphocyte count of only 1180 lymphocytes/µl.

At 1.5 months after treatment initiation, patients previously treated with fingolimod reached a minimum of 748 lymphocytes/µl. This value was clearly lower than that of naive patients (1238 lymphocytes/µl) and slightly lower than the minimum of platform patients (820 lymphocytes/µl). During the ongoing treatment course, patients treated with fingolimod experienced a steep recovery phase of lymphocyte counts. This resulted in a maximum count in the first year of 1107 lymphocytes/µl in month 12, which is 183 lymphocytes/µl lower than the count observed in naive patients.

In month 13.5, which was 1.5 months after the initiation of the second cladribine cycle, the lymphocyte count of fingolimod patients decreased to a minimum of 794 lymphocytes/µl. This count was higher than the minimum count observed in naive patients and patients receiving platform treatment.

Subsequently, the lymphocyte count recovered, reaching 1184 lymphocytes/µl in month 24. This count was now again higher than the lymphocyte count of naive and platform treated patients.

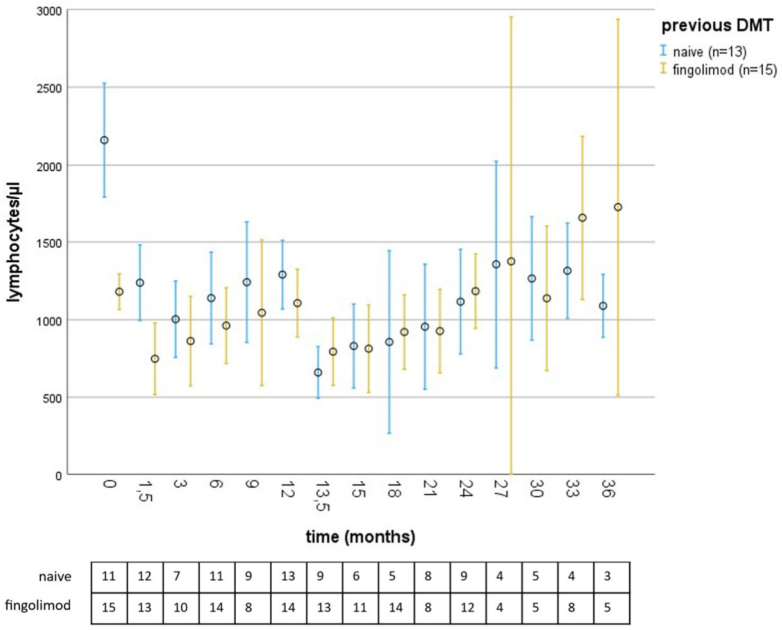


Figure 26: The graph shows a comparison between the lymphocyte counts of naive patients and patients pretreated with fingolimod. The remaining patients are shown in the table below. Patients previously treated with fingolimod showed markedly lower lymphocyte counts than naive patients initially. However, these counts then rose to comparable levels.

3.9.4 Natalizumab

The lymphocyte course of natalizumab patients could not be depicted in a graph due to a lack of lymphocyte data for patients previously treated with natalizumab (data were only available for 5 patients). However, it was observed that patients who received natalizumab had a markedly higher lymphocyte count at baseline compared to treatment-naive patients and those who received another disease-modifying therapy.

3.10 Cox Regression

Finally, a Cox regression analysis was conducted to identify parameters with a significant influence on the efficacy of cladribine treatment. The following parameters were considered: previous DMT (naive, platform therapy, fingolimod, natalizumab), number of previous DMTs, gender, age at baseline, MS duration since diagnosis, ARR at baseline, MRI progression at baseline, EDSS at baseline, and lymphocyte count at baseline. The efficacy of the treatment was evaluated based on the following dependent variables: time to first clinical relapse, time to first MRI progression, and time to first EDSS worsening. In order to achieve more precise results, only patients who had undergone treatment for three or more years were included in the study.

3.10.1 Time to first clinical relapse

Table 8: Cox regression analysis for time to first clinical relapse

Time to first clinical relapse (year 3+ patients)		HR	95% CI	p value
Last previous DMT	Naive	1.537	0.779-3.034	0.215
	Platform therapy	0.955	0.579-1.573	0.856
	Fingolimod	1.303	0.705-2.408	0.399
	Natalizumab	0.449	0.110-1.836	0.265
Number of previous DMTs		0.974	0.793-1.197	0.801
Male vs. female		0.894	0.476-1.679	0.728
Age at baseline (years)		0.991	0.967-1.014	0.434
MS duration since diagnosis (years)		0.999	0.996-1.002	0.449
ARR at baseline		**1.269**	**1.064-1.514**	**0.008**
MRI progress at baseline		1.352	0.751	2.434
EDSS at baseline		1.073	0.928-1.240	0.342
Lymphocyte count (/µl)		1.000	1.000-1.000	0.964

The initial model (Table 8) concerning the time to first clinical relapse identified a high annual relapse rate at baseline as a significant risk factor for the occurrence of a clinical relapse. Conversely, a low relapse rate at baseline appears to exert a favourable influence on the relapse course during cladribine treatment. (HR=1.269, p=0.008)

3.10.2 Time to first MRI lesion

Table 9: Cox regression analysis for time to first MRI progression

Time to first MRI lesion (year 3+ patients)		HR	95% CI	p value
Last previous DMT	**Naive**	**1.953**	**1.005-3.796**	**0.048**
	Platform therapy	0.995	0.585-1.690	0.984
	Fingolimod	0.845	0.413-1.729	0.645
	Natalizumab	0.720	0.175-2.956	0.648
Number of previous DMTs		0.913	0.721-1.157	0.450
Male vs. female		0.673	0.329-1.378	0.279
Age at baseline (years)		**0.971**	**0.946-0.998**	**0.034**
MS duration since diagnosis (years)		0.997	0.993-1.000	0.081
ARR at baseline		1.038	0.825-1.306	0.751
MRI progress at baseline		**3.078**	**1.386-6.835**	**0.006**
EDSS at baseline		0.893	0.737-1.082	0.249
Lymphocyte count (/µl)		1.000	1.000-1.000	0.863

The second model (Table 9) yielded comparable results. The analysis demonstrated that an MRI progress at baseline is a significant risk factor for subsequent MRI lesions following cladribine induction. Consequently, a stable MRI report at the commencement of treatment appears to act as a protective factor against the development of MRI lesions throughout the course of treatment (HR=3.078, *p*=0.006).

Furthermore, age was found to be a significant factor. The results of the Cox regression analysis indicated that age has only a minimal effect on the likelihood of developing MRI lesions throughout the treatment period (HR=0.971, p=0.034). Therefore, a younger age at baseline was associated with only a slightly higher likelihood of developing MRI lesions, while an older age was associated with a slightly lower possibility of developing MRI lesions.

Finally, the pre-treatment appeared to be a crucial factor. Naive patients seemed to be at a significantly higher risk for developing a new T2 lesion during the treatment course than patients who had been previously treated with a DMT (HR=1.953, *p*=0.048). This issue will be addressed in greater detail in the subsequent discussion.

3.10.3 Time to first EDSS worsening

Table 10: Cox regression analysis for time to first EDSS worsening

Time to first EDSS worsening (year 3+ patients)		HR	95% CI	p value
Last previous DMT	Naive	0.617	0.145-2.626	0.513
	Platform therapy	1.338	0.628	2.852
	Fingolimod	1.854	0.809-4.249	0.145
	Natalizumab	0.516	0.069-3.858	0.519
Number of previous DMTs		1.243	0.927-1.667	0.146
Male vs. female		1.824	0.818-4.068	0.142
Age at baseline (years)		0.996	0.962-1.031	0.826
MS duration since diagnosis (years)		1.000	0.995-1.005	0.972
ARR at baseline		0.859	0.581-1.269	0.445
MRI progress at baseline		0.832	0.367-1.885	0.660
EDSS at baseline		1.009	0.800-1.273	0.941
Lymphocytes (/µl)		1.000	0.999-1.000	0.325

A final Cox regression (Table 10) was performed to examine the time to first EDSS worsening. Nevertheless, no variables were identified that exerted a significant influence on the time to first EDSS worsening.

4. Discussion

This study provides comprehensive data on cladribine treatment from a retrospective real-world dataset comprising 167 MS patients from a university hospital and three established neurological practices. The objectives of this study were to evaluate the clinical efficacy, adverse effects and predisposing factors associated with the successful treatment of cladribine. By collecting data regarding relapse rates, MRI and EDSS, the study investigated the efficacy of cladribine over a period of up to five years (MRI and EDSS) / six years (ARR). As demonstrated in previous studies, cladribine resulted in a notable reduction in annual relapse rates and MRI progression. However, a minor EDSS deterioration was observed throughout the course of the disease in patients undergoing cladribine treatment.

Furthermore, the occurrence of side effects, including lymphocyte counts, was documented in order to assess the safety of cladribine tablets in a real-world setting. During the observation period, no severe adverse events were observed, and only two patients experienced grade IV lymphopenia following the second treatment administration.

Finally, the study aimed to identify risk or protective factors that have a significant impact on the course of the disease under cladribine treatment. The results demonstrated that a low relapse activity at baseline exerts a positive influence on the relapse course, whereas a low MRI activity at baseline exerts a protective impact on the MRI progression course under cladribine treatment. Moreover, patients who were naive to the treatment were more likely to develop an early MRI lesion following the initiation of cladribine, a topic that will be addressed subsequently. Nevertheless, no significant effects were observed on the EDSS course.

In summary, the baseline characteristics of our cohort were comparable to those observed in the CLARITY trial from 2010 [Giovannoni et al., 2010] and in the real-world cohort from 2022 [Pfeuffer et al., 2022].

The median age was slightly lower (median: 34 vs. 39 in the real-world cohort from 2022), while the gender distribution was slightly shifted towards a higher proportion of females (proportions of females: 79% vs. 61% in the real-world

cohort from 2022 vs. 68.8% in the CLARITY study population). However, the median disease duration since diagnosis was markedly lower in our cohort (median disease duration since diagnosis: 75 months vs. 4 years in the real-world population). Furthermore, efficacy parameters were comparable, with a median annual relapse rate and EDSS at baseline similar to those observed in the real-world cohort study from 2022. It should be noted that the method used to record MRI lesions at baseline differed from that employed in the other studies, which precludes a direct comparison. In comparison to the real-world cohort from 2022, our cohort comprised patients with a higher number of previous disease-modifying therapies (DMTs) as well as a lower proportion of treatment-naive patients (median number of previous DMTs: 2 vs. 1 in the real-world cohort from 2022; proportion of naive patients: 13.8% vs. 36% in the real-world cohort from 2022). With regard to previous treatment, the cohort comprises the aforementioned naive patients (13.8%), patients who have received a DMT more than one year prior to cladribine initiation (10.8%), and 75.4% of patients who have received a DMT less than one year prior to cladribine start. The majority of patients have received one previous DMT (35.3%). Among patients who had received a DMT within the one-year period prior to cladribine initiation, the majority had received a platform therapy (64.3%). Furthermore, the most common reasons for treatment switch were due to clinical or MRI progression (52%). In contrast, the real-world cohort from 2022 exhibited a majority of patients who had not received any prior treatment (36%), while patients previously treated with one DMT constituted only the second largest proportion (27%).

In terms of efficacy, the results obtained were in accordance with those of previous studies. In comparison to the one-year period prior to the initiation of cladribine treatment, the relapse course from year one to year six showed a significant reduction in relapse rates. Similarly, a notable reduction in the number of patients presenting with new T2 lesions in comparison to the one-year period preceding cladribine induction was observed during the treatment years one to five. Although the EDSS score remained relatively stable, there was a slight increase in EDSS rates, with a peak in year 4.

With regard to adverse events, a total of 64 patients (38.3%) reported an

unwanted event following the first or second administration of cladribine. Of the adverse events reported, headaches (24%) and fatigue (19%) were the most frequently cited. In comparison to the CLARITY study in 2010, where 47.7% of the patients suffered from an infection or infestation, only 20% of the reported side effects were due to infections in our cohort. Nevertheless, twelve patients reported a herpes zoster infection, while four patients reported an oral herpes infection. Moreover, in contrast to the CLARITY 2010 study, no patient in our cohort suffered from a severe adverse event or a neoplasm. This discrepancy between our cohort and the CLARITY study regarding some adverse events can be attributed to the nature of the study design. In a real-world cohort, only side effects that are reported by patients to their neurologist are included in the study, which may result in a less comprehensive report of adverse events. [Giovannoni et al., 2010]

In terms of lymphocyte counts, a notable decline was observed following the initial and second cladribine administrations. Following the initial administration, a minimum was observed in month 3, with a median of 800 lymphocytes/µl. Following the second administration, a minimum was observed in month 1.5, with a median of 570 lymphocytes/µl. However, in our cohort, a greater proportion of patients were spared from the phenomenon of lymphopenia than in the real-world cohort from 2022. While 21.26% of patients after the first administration and 10.24% of patients after the second administration did not suffer from lymphopenia, only 0.7% of patients in the real-world cohort from 2022 did not suffer from lymphopenia. In contrast, a lower proportion of patients exhibited grade I or II lymphopenia following the initial or second administration in our cohort. However, following the second treatment application, a markedly higher proportion of patients in our cohort exhibited grade III lymphopenia than in the real-world cohort from 2022 (33.86% in our cohort vs. 17.8% in the real-world cohort from 2018). While no grade IV lymphopenia was observed following the initial administration, a similar result was achieved following the second administration, with two patients (1.57%) experiencing a grade IV lymphopenia (vs. 1.1% in the real-world-cohort from 2022). It is important to note that in the real-world cohort from 2022, the proportions of lymphopenia grades in years 1

and 2 were merged, which makes comparison more challenging. [Pfeuffer et al., 2022].

Furthermore, the results of the real-world cohort from 2022 indicate that patients who had been treated with dimethyl fumarate prior to the study experienced a markedly stronger decrease in lymphocytes than naive patients and patients who had been treated with glatiramer acetate, beta-interferon or teriflunomide. These findings are consistent with those observed in our cohort, where dimethyl fumarate demonstrated a lymphocyte count of 120 lymphocytes/µl less than other platform treatments, and even 538 lymphocytes/µl less than naive patients at month 1.5. However, in contrast to the real-world cohort in 2022, the baseline lymphocyte count of patients receiving dimethyl fumarate was already decreased (1311 lymphocytes/µl vs. 1712 lymphocytes/µl in other platform therapies). In conclusion, the aforementioned findings indicate that dimethyl fumarate may be a risk factor for lymphopenia following the initiation of cladribine therapy. [Pfeuffer et al., 2022].

Another discrepancy is evident in the number of patients who have switched from cladribine to another DMT. In the real-world cohort from 2022, only three patients switched to another DMT. In contrast, 18 patients (10.78%) switched to another DMT in our cohort. In the real-world cohort, all three patients switched to ocrelizumab. [Pfeuffer et al., 2022]. Similarly, ocrelizumab was the most frequently selected DMT (66.7%) in our cohort. The most common year for treatment switch was year 4 (38.9%), while the most common reasons for switching were clinical or MRI progression or both (88.9%).

As previously stated, the objective of our study was to identify the factors that influence the disease course and efficacy of cladribine medication. In the initial phase of the study, the proportions of patients who did not experience a clinical event (relapse, MRI progression, or EDSS worsening) were observed over time, with stratification according to previous disease-modifying treatment.

With regard to the relapse course, natalizumab appeared to have the most favourable disease course (57.1% of patients without an event until year 5), while fingolimod showed the least favourable disease course (45% of patients without an event until year 5). The disease course of the platform therapy and naive

patients (52% of patients without an event until year 5 for platform therapy) is situated between the aforementioned categories. The individual platform therapies exhibited a similar course, with the exception of teriflunomide, which demonstrated a slightly superior performance (68.2% of patients without an event until year 5). This observation contrasts with the findings of the real-world cohort in 2022, in which natalizumab patients exhibited the poorest outcomes, while those receiving platform therapy demonstrated the most favourable outcomes. It is nevertheless important to note that the survival analysis in the real-world cohort from 2022 only extended until treatment month 48. Consequently, it is not possible to make comparisons for outcomes beyond that time. [Pfeuffer et al., 2022].

Furthermore, it is noteworthy that the outcomes of the MRI course exhibited a divergent pattern. In our cohort, natalizumab patients exhibited the poorest outcomes (35.7% of patients without an event until year 5), comparable to those of naive patients (35.7% of patients without an event until year 4). However, fingolimod demonstrated the most favourable outcome (59% of patients without an event until year 5), closely followed by platform therapy (55.4% of patients without an event until year 5). The outcomes of individual platform therapy exhibited a considerable degree of variability. While beta interferon demonstrated the most favorable results (83% of patients remained free of events until year 5), dimethyl fumarate patients exhibited the least favorable outcomes (41.1% of patients remained free of events until year 5). The results of the natalizumab treatment were comparable to those observed in the real-world cohort from 2022, in which natalizumab demonstrated the poorest outcomes aswell. Despite the unfavourable outcome, patients receiving natalizumab in our cohort demonstrated a more favourable MRI course than those in the real-world cohort from 2022 (the natalizumab curve ceased in month 24). However, in this cohort, fingolimod demonstrated a markedly inferior performance compared to that observed in our cohort. Conversely, naive patients exhibited markedly superior outcomes than in our cohort. A comparable unfavourable outcome was observed with the platform treatment dimethyl fumarate. [Pfeuffer et al., 2022].

The outcomes in our cohort with worsening EDSS resemble those observed in

relapse progression. Once more, natalizumab demonstrated the most favourable outcomes (75% of patients remained free of events until year 5), whereas fingolimod exhibited the least favourable course (47.4% of patients remained free of events until year 5). Similarly, these findings contrast with those of the real-world cohort from 2020, in which natalizumab performed the poorest. Fingolimod, which performed second worst in this cohort, still exhibited a markedly inferior outcome compared to that observed in our cohort. [Pfeuffer et al., 2022].

To elucidate the substantial discrepancies between the two cohorts, it is essential to acknowledge that our analysis encompassed merely 10 natalizumab patients, which may have influenced the statistical outcome. Furthermore, it is noteworthy that the natalizumab cohort exhibited the longest disease duration, which may have a certain impact on the outcome.

The aforementioned results also influenced the final screening for risk or protective factors. While natalizumab was identified as a significant risk factor for the relapse course, the MRI progression course, and the EDSS worsening course in the real-world cohort in 2022, the same results could not be found in our cohort. [Pfeuffer et al., 2022]. Instead, natalizumab appeared to exert a positive influence on the aforementioned efficacy parameters. However, these results were not statistically significant.

Furthermore, we identified additional protective factors: a low annual relapse rate at baseline for a favourable course of relapse rates and no MRI progression at baseline for a favourable course of MRI lesions. However, treatment-naive patients appeared to be at higher risk for MRI lesion progression. One potential explanation for this finding is that the naive patients represented the group with the shortest disease duration (median: 2.5 months). As demonstrated in numerous studies, the disease activity (relapse rates, MRI progression) of multiple sclerosis tends to decrease with the progression of the disease, leading to the conclusion that patients with a longer disease course are more likely to exhibit less disease activity than patients with a newly diagnosed MS [Doshi et al., 2016]; [Cree et al., 2019]. Subsequently, patients who have undergone prior treatment and thus have a longer disease duration are less likely to exhibit early

activity than those who are treatment-naïve. This may explain why the Cox regression analysis identified the latter group as a risk factor for early activity.

In conclusion, the results suggest that, although our cohort shows a favourable outcome for patients with low clinical and paraclinical disease activity at baseline, treatment choice is dependent on multiple variables. Consequently, our study is unable to completely discern a specific pattern among patients who exhibit a favourable treatment response to cladribine.

It should be noted that certain limitations exist. Firstly, it should be noted that the data used in this study is retrospective and obtained from a real-world cohort. This makes the detection of efficacy parameters and adverse events more challenging, as well as dependent on the compliance of patients and the documentation of the responsible neurologists. Nevertheless, our cohort comprises a substantial amount of data on the efficacy course and adverse events of cladribine patients due to the frequent follow-up examinations conducted in each centre.

In conclusion, cladribine is an efficacious disease-modifying treatment that markedly reduces the clinical and paraclinical manifestations of the multiple sclerosis disease course. Although the treatment predominantly results in lymphopenia, this is generally mild and does not lead to any other severe adverse events. Individuals who are at a low clinical and paraclinical activity level at baseline are more likely to respond positively to treatment with cladribine. With regard to the third cycle of cladribine in year five, it is of the vital importance to collect long-term data on the cladribine patients in order to further evaluate the necessity of another treatment administration for efficacy and to detect the possible adverse events.

5. Summary

The objective of this study was to evaluate the clinical efficacy, adverse events and predisposing factors associated with a successful treatment response to cladribine. Data on relapse rates, MRI and EDSS scores over a period of up to five (MRI and EDSS) and six years (ARR), as well as adverse events and lymphocyte counts were collected retrospectively. Furthermore, baseline data characteristics were assessed in order to identify additional parameters that may influence the efficacy of cladribine treatment.

Descriptive statistics were employed to illustrate the baseline data, efficacy and side effects associated with cladribine treatment. The results showed the following finding: First, treatment with cladribine was observed to result in a significant reduction in the annual relapse rate and MRI progression. Nevertheless, the EDSS scores exhibited minimal fluctuation, with a slight increase observed in several patients. Furthermore, apart from the typical adverse effects associated with cladribine, no severe adverse events were observed. Only two patients exhibited grade 4 lymphopenia, which did not result in any significant complications. With regard to the various prior treatments, dimethyl fumarate pre-treatment demonstrated the most pronounced influence on the risk of lymphopenia among all platform treatments.

To evaluate the effects of prior treatments on the efficacy of cladribine treatment, Kaplan-Meier curves were utilized. This analysis revealed notable discrepancies in the efficacy trajectory between different pre-treatments. However, a subsequent Log-Rank test indicated that the pre-treatment did not exert a significant impact on the time to a first event (relapse, MRI progression, EDSS worsening).

Finally, a Cox regression analysis was employed to ascertain the pivotal risk and protective factors influencing the efficacy of the cladribine treatment course. A low annual relapse rate at baseline was identified as a protective factor for early relapses, and a low MRI progression at baseline was identified as a protective factor for early MRI progression in the disease course. Furthermore, pre-treatment appeared to serve as a protective factor for the occurrence of early MRI

activity. However, this finding may be attributed to the longer disease duration observed in this group, as well as the concomitant lower clinical activity. In conclusion, the choice of treatment depends on many variables and our study cannot fully identify a specific pattern among patients with a favourable response, but we can provide some guidance on the efficient use of cladribine in clinical routine.

5.1 Zusammenfassung

Ziel dieser Studie war es, die klinische Wirksamkeit, unerwünschte Ereignisse und prädisponierende Faktoren im Zusammenhang mit einem erfolgreichen Ansprechen auf die Behandlung mit Cladribin zu untersuchen. Daten zu Schubraten, MRT- und EDSS-Scores über einen Zeitraum von bis zu fünf (MRI und EDSS) und sechs Jahren (ARR) sowie unerwünschte Ereignisse und Lymphozytenzahlen wurden retrospektiv erfasst. Darüber hinaus wurden Baseline-Daten gesammelt, um zusätzliche Parameter zu identifizieren, die die Wirksamkeit von Cladribin-Behandlungen beeinflussen könnten.

Zunächst wurden deskriptive Statistiken verwendet, um die Baseline-Daten, die Wirksamkeit und die Nebenwirkungen der Cladribin-Behandlung zu veranschaulichen. Die Ergebnisse führten zu folgenden Ergebnissen: Zum einen wurde beobachtet, dass die Behandlung mit Cladribin zu einer signifikanten Verringerung der jährlichen Schubrate und des MRT-Progresses führte, während der EDSS trotz eines nahezu konstanten Verlaufs einen leichten Anstieg verzeichnete. Darüber hinaus wurden, abgesehen von den typischen Nebenwirkungen, im Zusammenhang mit Cladribin keine schweren unerwünschten Arzneimittelnebenwirkungen beobachtet. Nur zwei Patienten wiesen eine Lymphopenie Grad 4 auf, die zu keinen signifikanten Komplikationen führte. Im Hinblick auf die verschiedenen Vortherapien zeigte die Dimethylfumarat-Vortherapie den größten Einfluss auf das Risiko einer Lymphopenie unter Cladribin verglichen mit allen Plattformtherapien.

Um den Einfluss der Vortherapien auf die Wirksamkeit der Cladribin-Behandlung zu bewerten, wurden Kaplan-Meier-Kurven verwendet. Diese Analyse ergab bemerkenswerte Diskrepanzen im Wirksamkeitsverlauf zwischen verschiedenen Vorbehandlungen. Ein anschließender Log-Rank-Test zeigte jedoch, dass die Vorbehandlung keinen signifikanten Einfluss auf die Zeit bis zu einem ersten Ereignis (Schub, MRT-Progression, EDSS-Verschlechterung) hatte.

Schließlich wurde eine Cox-Regressionsanalyse durchgeführt, um die zentralen Risiko- und Protektiv-Faktoren zu ermitteln, die die Wirksamkeit des Cladribin-Behandlungsverlaufs beeinflussen. Eine niedrige jährliche Schubrate zu Studienbeginn wurde als Schutzfaktor für frühe Schübe identifiziert, während eine niedrige MRT-Progression zu Studienbeginn als Schutzfaktor für eine frühe MRT-Progression im Krankheitsverlauf identifiziert wurde. Darüber hinaus schien das Vorhandensein einer Vortherapie als Schutzfaktor für das Auftreten einer frühen MRT-Aktivität zu dienen. Dieser Befund könnte jedoch auf die in dieser Gruppe beobachtete längere Krankheitsdauer sowie die damit einhergehende geringere klinische Aktivität zurückgeführt werden.

Zusammenfassend ist die Wahl der Behandlung von vielen Variablen abhängig und unsere Studie kann kein umfassendes, spezifisches Muster für Patienten mit günstigem Ansprechen identifizieren. Einige wichtige Hinweise für den effizienten Einsatz von Cladribin in der klinischen Routine können jedoch abgeleitet werden.

6. List of References

- Comi G, Cook S, Giovannoni G, Rieckmann P et al. (2019): Effect of cladribine tablets on lymphocyte reduction and repopulation dynamics in patients with relapsing multiple sclerosis, in Multiple Sclerosis and Related Disorders; 29: p. 168-174
- Correale J, Gaitán M, Ysrraelit M, Fiol M (2017): Progressive multiple sclerosis: from pathogenic mechanisms to treatment, in Brain; 140: p. 527-546
- Cree B, Hollenbach J, Bove R, Kirkish G et al. (2019): Silent progression in disease activity–free relapsing multiple sclerosis, in Annals of Neurology; 85: p. 653-666
- Deeks E (2018): Cladribine Tablets: A Review in Relapsing MS, in CNS Drugs; 32: p. 785-196
- Dobson R, Giovannoni G (2019): Multiple sclerosis – a review, in European Journal of Neurology; 26: p. 27-40
- Doshi A, Chataway J (2016): Multiple sclerosis, a treatable disease, in Clinical Medicine; 16: p. 53-59
- Giovannoni G, Mathews J (2022): Cladribine Tablets for Relapsing–Remitting Multiple Sclerosis: A Clinician's Review, in Neurology and Therapy; 11: p. 571-595
- Giovannoni G, Soelberg P, Cook S, Rammohan K 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, in Multiple Sclerosis Journal; 24: p. 1594-1604
- Giovannoni G, Comi G, Cook S, Rammohan K et al. (2010): A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis, in New England Journal of Medicine; 362: p. 416-426
- Hauser S, Cree B (2020): Treatment of Multiple Sclerosis: A Review, in The American Journal of Medicine; 133: p. 1380-1390

- Leist T, Cook S, Comi G, Montalban X et al. (2020): Long-term safety data from the cladribine tablets clinical development program in multiple sclerosis, in Multiple Sclerosis and Related Disorders; 46
- Leist T, Comi G, Cree B, Coyle B et al. (2014): Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial, in The Lancet Neurology; 13: p. 257-267
- Moccia M, Lanzillo R, Petruzzo M, Nozzolillo A et al. (2020): Single-Center 8-Years Clinical Follow-Up of Cladribine-Treated Patients From Phase 2 and 3 Trials, in Frontiers in Neurology; 11: p. 489
- Moser T, Ziemssen T, Sellner J (2022): Real-world evidence for cladribine tablets in multiple sclerosis: further insights into efficacy and safety, in Wiener Medizinische Wochenschrift (1946); 172: p. 365-372
- Pfeuffer S, Rolfes L, Hackert J, Kleinschnitz K et al. (2022): Effectiveness and safety of cladribine in MS: Real-world experience from two tertiary centres, in Multiple Sclerosis Journal; 28: p. 257-268
- Rammohan K, Giovannoni G, Comi G, Cook S et al. (2012): Cladribine tablets for relapsing–remitting multiple sclerosis: Efficacy across patient subgroups from the phase III CLARITY study, in Multiple Sclerosis and Related Disorders; 1: p. 49-54
- Rudrapatna V, Butte A (2020): Opportunities and challenges in using real-world data for health care, in The Journal of Clinical Investigation; 130: p. 565-574
- Selmaj K, Cree B, Barnett M, Thompson A, Hartung H (2024): Multiple sclerosis: time for early treatment with high-efficacy drugs, in Journal of Neurology; 271: p. 105-115
- Thompson A, Banwell B, Barkhof F, Carroll W et al. (2018): Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria, in The Lancet Neurology; 17: p. 162-173
- Yamout B, Alroughani R (2018): Multiple Sclerosis, in Seminars in Neurology; 38: p. 212-225

7. Declaration of own contribution

The research was conducted at the University Hospital of Tübingen, Department of Neurology, under the supervision of apl. Prof. Dr. M. Kowarik.

The study concept was developed in collaboration with the established neurologist Michael Ernst and other established neurologists (Dr. Benedicta Kühnler, Dr. Sylke Schlemilch-Paschen, Dr. Lukas Cepek, Dr. Daniela Rau)

On the one hand, I was responsible for the organisation of the project. This included preparing an ethics application for the University Hospital of Tübingen and the Baden-Württemberg Medical Association, defining the parameters to be collected and supporting the practices in collecting the data.

Moreover, I was responsible for the planning and execution of the statistical analysis, in accordance with the guidance provided by the Institute of Biometry.

I confirm that I have written the manuscript entirely on my own under the supervision of apl. Prof. Dr. M. Kowarik and that I have not used any quotations other than those provided.

Tübingen,