RESEARCH ARTICLE OPEN ACCESS

The Italian Multiple Sclerosis Register Experience With Cladribine

Impact on Relapses, PIRA, and Treatment Sequencing Strategies Evaluation

Tommaso Guerra,[1] Massimiliano Copetti,[2] Chiara Zanetta,[3] Francesco Patti,[4] Clara Grazia Chisari,[4] Elena Barbuti,[5] Emilio Portaccio,[6] Matteo Foschi,[7,8] Antonella Conte,[9,10] Diana Ferraro,[11] Eleonora E. Cocco,[12] Roberta Fantozzi,[10] Giorgia Teresa Maniscalco,[13] Giuseppe Salemi,[14] Carla Tortorella,[15] Damiano Paolicelli,[1] Massimo Filippi,[3,16] Maria Pia Amato,[6,17] Maria Trojano,[1] and Pietro Iaffaldano,[1] for the Italian Multiple Sclerosis & Related Disorders Register (RISM)

Correspondence
Dr. Iaffaldano
pietro.iaffaldano@uniba.it

Neurol Neuroimmunol Neuroinflamm 2025;12:e200415. doi:10.1212/NXI.0000000000200415

Abstract

Background and Objectives

Cladribine is an immune reconstitution therapy approved for relapsing multiple sclerosis (RMS). This multicentric retrospective study of the Italian Multiple Sclerosis Register (RISM) aimed to assess the effect of cladribine on the annualized relapse rate (ARR) and progression independent of relapse activity (PIRA) phenomena, also evaluating the strategies of disease-modifying treatment (DMT) continuation after cladribine termination.

Methods

Patients with RMS treated with at least one cycle of cladribine recorded in RISM after 2018 were retrospectively included in the analysis. Patients previously treated with other DMTs were stratified into moderately and highly effective DMTs. Adjusted ARR and PIRA events were calculated in the overall cohort and stratified by age at cladribine start (<50 vs ≥ 50 years) and by previous DMT. ARRs were compared between groups using negative binomial models. PIRA was analyzed using the Ghosh-Lin Cox-type regression for the marginal mean. DMTs prescribed after cladribine cycles were analyzed.

Results

A total of 2,329 patients treated with cladribine were identified in RISM, with a median (IQR) age of 36.5 (29.2–45.2) years at treatment start. 1,488 patients (63.9%) received 2 courses of cladribine. ARR decreased ($p < 0.0001$) from 0.96 (95% CI 0.91–1.02) in the 2 years preceding cladribine start to 0.09 (0.08–0.11) during the 2 years after in the overall cohort. One hundred thirty-three PIRA events were reported during the noncladribine treatment period and 54 during cladribine therapy (HR 0.711, 95% CI 0.531–0.952, $p = 0.0219$) in the entire cohort. All the analyses stratified by age and previous treatment confirmed the significant reduction in PIRA events and the suppression of relapse activity. After cladribine, most DMTs prescribed were ocrelizumab, ofatumumab, and natalizumab. Eight patients re-treated with an additional cycle of cladribine were also identified.

Discussion

For patients with RMS, both naïve and switchers, as well as younger and older patients, cladribine is an effective treatment in reducing relapses and PIRA. Different therapeutic strategies after cladribine are currently reported.

MORE ONLINE

Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

[1]Department of Translational Biomedicine and Neurosciences, University of Bari "Aldo Moro", Italy; [2]Unit of Biostatistics, Fondazione IRCCS –"Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy; [3]IRCCS San Raffaele Scientific Institute, Milan, Italy; [4]Dipartimento di Scienze Mediche e Chirurgiche e Tecnologie Avanzate, GF Ingrassia, University of Catania, Italy; [5]Department of Human Neurosciences, Sapienza University of Rome, Italy; [6]Department of Neurofarba, University of Florence, Italy; [7]Department of Neuroscience, Multiple Sclerosis Center-Neurology Unit, S.Maria delle Croci Hospital, AUSL Romagna, Ravenna, Italy; [8]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy; [9]Department of Human Neurosciences, Sapienza, University of Rome, Rome, Italy; [10]IRCCS Neuromed, Pozzilli, Italy; [11]Department of Neurosciences, Ospedale Civile di Baggiovara, Azienda Ospedaliero-Universitaria di Modena, Italy; [12]Department of Medical Science and Public Health, University of Cagliari, Italy; [13]Multiple Sclerosis Regional Center, "A. Cardarelli" Hospital, Naples, Italy; [14]Department of Biomedicine, Neurosciences and Advanced Diagnostics, University of Palermo, Italy; [15]Hospital San Camillo-Forlanini, Rome, Italy; [16]Vita-Salute San Raffaele University, Milan, Italy; and [17]IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy.

The Article Processing Charge was funded by the authors.

Glossary

ARR = annualized relapse rate; **DMT** = disease-modifying treatment; **FSs** = functional scores; **HE** = highly effective; **IQR** = interquartile range; **IRT** = immune reconstitution therapy; **ME** = moderately effective; **MS** = multiple sclerosis; **OCB** = oligoclonal band; **PIRA** = progression independent of relapse activity; **RISM** = Italian Multiple Sclerosis Register; **RMS** = relapsing multiple sclerosis.

Classification of Evidence

This study provides Class IV evidence that for patients with relapsing multiple sclerosis, cladribine treatment is associated with a reduction in ARR and PIRA events.

Introduction

Immune reconstitution therapy (IRT), administered in short dose intervals to produce durable immunologic effects, has transformed multiple sclerosis (MS) management into the constantly evolving repertoire of disease-modifying treatments (DMTs), providing an additional treatment contributing to the prevention of the irreversible disability accrual related to MS.[1-3]

Cladribine is an oral selective IRT, a synthetic analog of deoxyadenosine that causes a rapid and temporary depletion of lymphocytes followed by a process of immune reconstitution, with a modest impact on the innate immune system.[4,5] Cladribine tablets were approved by the European Medical Agency in August 2017 and are refundable in Italy for the treatment of adults with highly active relapsing multiple sclerosis (RMS), as defined by clinical and MRI features. The unique immune cell dynamics may explain the efficacy and safety profile of cladribine tablets: requiring only 2 treatment courses in 2 years has revolutionized the therapeutic paradigms and the life quality of patients with MS.[6] The CLARITY (CLAdRIbine Tablets treating multiple sclerosis orallY) and CLARITY Extension studies examined the safety and effectiveness profile of cladribine, showing significant improvements in relapse rate, disability progression, and MRI parameters of disease activity, in parallel with an excellent safety profile.[7-9] A growing amount of real-world evidence reinforced the strong anti-inflammatory effect of cladribine, highlighting the sustained efficacy related to the reconstitution of immune cells.[10-13]

Formerly believed to be limited to the later stages of the disease, progression independent of relapse activity (PIRA) events have been amply identified even in the earliest stages, outlining a disease *continuum* of neuroinflammation and neurodegeneration processes.[14,15] Therefore, it is crucial to investigate how DMTs may affect PIRA events and, by extension, the underlying phenomena.

Over the past few years, an increasing number of studies derived from the real-world dataset of the Italian MS and Related Disorders Register (RISM) have demonstrated the ability to address and overcome the most debated topics in MS research arising from routine clinical practice.[16-18]

In this study, we aimed to assess the effect of cladribine on the annualized relapse rate (ARR) and PIRA events in the Italian cladribine-treated cohort in the RISM. We also evaluated the strategies of DMT continuation after cladribine termination recorded in the RISM.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The RISM was approved by the ethical committee at the "Azienda Ospedaliero—Universitaria—Policlinico of Bari" (Study REGISTRO SM001—approved on July 8, 2016) and by local ethics committees in all participating centers. Patients signed informed consent that allows collection and use of their clinical data for research purposes. According to the register rules, the Scientific Committee of the RISM granted the approval to conduct this project and extract and use the registry data.

Data Extraction

This was a study based on data extracted from the RISM. Data extraction was executed in March 2024. A minimum dataset of demographic and clinical characteristics from RISM was considered.

Study Population

Patients with RMS treated with at least one cycle of cladribine recorded in RISM after January 1, 2018, were retrospectively included in the analysis. Only patients in the RISM with consistent data were included, excluding patients with errors or incongruences in their clinical history.

Patients previously treated with other DMTs were stratified into moderately effective (ME) and highly effective (HE) DMTs.[19] The following treatments were classified as ME DMTs: azathioprine, dimethyl fumarate, glatiramer acetate, interferon-beta products, and teriflunomide. The following products were considered HE DMTs: alemtuzumab,

fingolimod, mitoxantrone, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, and rituximab.

Study Method and Statistical Analysis

The following variables were included in the dataset: age (in years), sex (male and female), type of onset (monofocal/multifocal/not known), IgG oligoclonal bands (OCBs) in the CSF (presence/absence/not known), number of EDSS evaluations with complete information regarding functional scores (FSs), start and end dates of all the administered DMTs, and number and dates of relapses.

In descriptive analyses, categorical data were expressed as frequency and proportion. Continuous data were expressed as mean and SD or as median and interquartile range (IQR).

Relapses in the 2 years before and after cladribine initiation were assessed and compared using negative binomial regression models, and results were given as ARRs along with their 95% confidence intervals (95% CIs).[20] The analyses were performed in the whole population and stratified by age at cladribine start (<50 vs ≥ 50 years) and by previous DMT (ME vs HE DMTs).

To ensure reliability of results, PIRA was analyzed in a subgroup of patients with complete and carefully checked start and end dates of every week of cladribine treatment.

PIRA was considered as a recurrent event through the follow-up. PIRA was defined as a sustained (for the remaining recorded follow-up time) progression of disability, confirmed at 6 months, in the absence of a relapse since 90 days before the EDSS evaluation with documented increase.[21] Cladribine was considered as a time-dependent exposure. Time variable was defined as the time between the baseline visit and the end of follow-up. PIRA was, therefore, analyzed using the Ghosh-Lin Cox-type regression for the marginal mean. Risks were reported as hazard ratios (HRs) along with their 95% CIs and p values. Furthermore, an interaction term (cladribine treatment-by-covariate) was added into the model to explore potential differential efficacy between clinical and/or demographic subgroups.

The proportion of patients without PIRA events (PIRA-free probability) stratified based on the time-dependent exposure to cladribine over the entire follow-up period was shown using Kaplan-Meier curves.

A sensitivity analysis was also performed including only the subset of patients who received 2 cycles of cladribine.

A p value less than 0.05 was considered as statistically significant. All analyses were performed using R (version 4.2.0, R Foundation for Statistical Computing, Vienna, Austria).

Table 1 Baseline Demographic and Clinical Characteristics

Variable	N = 2,329
Female sex, n (%)	1,654 (71)
Age at onset (mean ± SD), y	29.47 ± 9.59
Age at diagnosis (mean ± SD), y	31.42 ± 9.72
Time from onset to diagnosis (mean ± SD), y	1.97 ± 3.66
Age at first cladribine cycle start (mean ± SD; median [IQR]), y	37.45 ± 10.61; 36.5 (29.2–45.2)
Time from onset to first visit (mean ± SD), y	2.96 ± 4.99
Presence of CSF IgG oligoclonal bands, n (% of the total available data, 1,410 cases)	1,156 (82)
Number of cerebrospinal fluid IgG oligoclonal bands, median (IQR)	10 (1–33)
Disease duration at the time of the analysis (mean ± SD), y	10.78 ± 8.0
Age at the time of analysis (mean ± SD), y	40.21 ± 10.64
Updated patients (RISM-App codification), n (%)	1,915 (82.2)
Patients starting cladribine as first DMT, n (%)	679 (2,29)
Patients starting cladribine after ME DMTs, n (%)	1,321 (56.7)
Patients starting cladribine after HE DMTs, n (%)	329 (14.1)
Time between the last cladribine cycle and the following first DMT start (mean ± SD; median [IQR]), y (n = 268)	1.56 ± 1.04; 1.37 (0.82–2.26)
Follow-up after cladribine (from first start date to last update) in those patients not receiving a new DMT, y (n = 2,061)	1.77 ± 1.22; 1.7 (0.9–2.8)

Abbreviations: DMT = disease-modifying treatment; HE DMT = highly effective disease-modifying treatment; ME DMT = moderately effective disease-modifying treatment; RISM = Italian Multiple Sclerosis Register.

Data Availability

Anonymized data will be shared on reasonable request from a qualified investigator.

Results

Clinical data of 87,782 patients were available in the IMSR at the time of data extraction. After applying the inclusion criteria, we retrieved a cohort of 2,329 patients treated with at least one cycle of cladribine. The median (IQR) age at treatment start was 36.5 (29.2–45.2) years, and the median follow-up time after cladribine start was 1.7 (0.9–2.8) years; 71% (n = 1,654) were female. Table 1 lists the detailed demographic and clinical characteristics of the cohort. 1,488 patients (63.9%) received 2 courses of cladribine.

Treatment Patterns Before and After Cladribine

A total of 679 patients (29.1%) were treatment naïve, and 1,321 (56.7%) were previously treated with ME DMTs and 329 (14.1%) with HE DMTs. All previous DMTs administered before treatment with cladribine are presented in Table 2. The median time between the date of the suspension of the last recorded DMT and the first cladribine cycle was 1.4 (0.8–2.2) months.

The number of patients starting a new treatment after the last cycle of cladribine was 268, and the average time between the last cycle and the beginning of the next DMT was 1.56 (1.04) years, with a median of 1.37 (0.82–2.26) years. After cladribine termination, we identified 8 patients re-treated with an additional cycle of cladribine, 148 with an anti-CD20 treatment (92 with ocrelizumab, 54 with ofatumumab, 2 with rituximab), 46 with natalizumab, 39 with a S1P receptor-modulator (3 with fingolimod, 17 with ozanimod, 3 with ponesimod, 16 with siponimod), and 5 with alemtuzumab. A total of 45 patients were treated with ME DMTs (Table 3).

Treatment pathways are visualized in the Sankey plot illustrated in Figure 1.

ARR Evaluation

In the overall cohort, ARR decreased ($p < 0.0001$) from 0.96 (95% CI 0.91–1.02) in the 2 years preceding cladribine start to 0.09 (95% CI 0.08–0.11) during the 2 years after. All the analyses stratified by age and previous treatment confirmed the significant reduction of ARR ($p < 0.0001$), regardless of age at treatment start and previous DMT efficacy profile. Considering the age cutoff of 50 years, pretreatment ARR of 0.61 (0.52–0.73) in patients who started treatment at least at 50 years of age converted to a post-treatment ARR of 0.04 (0.02–0.06); pretreatment ARR of 1.01 (0.95–1.08) in patients who began treatment at an age younger than 50 years changed to a post-treatment ARR of 0.1 (0.09–0.12). In naïve patients, the pretreatment ARR was 1.66 (1.52–1.81), but after cladribine treatment, it dropped to 0.09 (0.07–0.12). A similar trend is seen in patients who had ME DMTs before cladribine treatment, with a change in ARR from 0.68 (0.63–0.74) to 0.07 (0.06–0.09) after treatment, and in patients treated with HE DMTs before cladribine, with a change

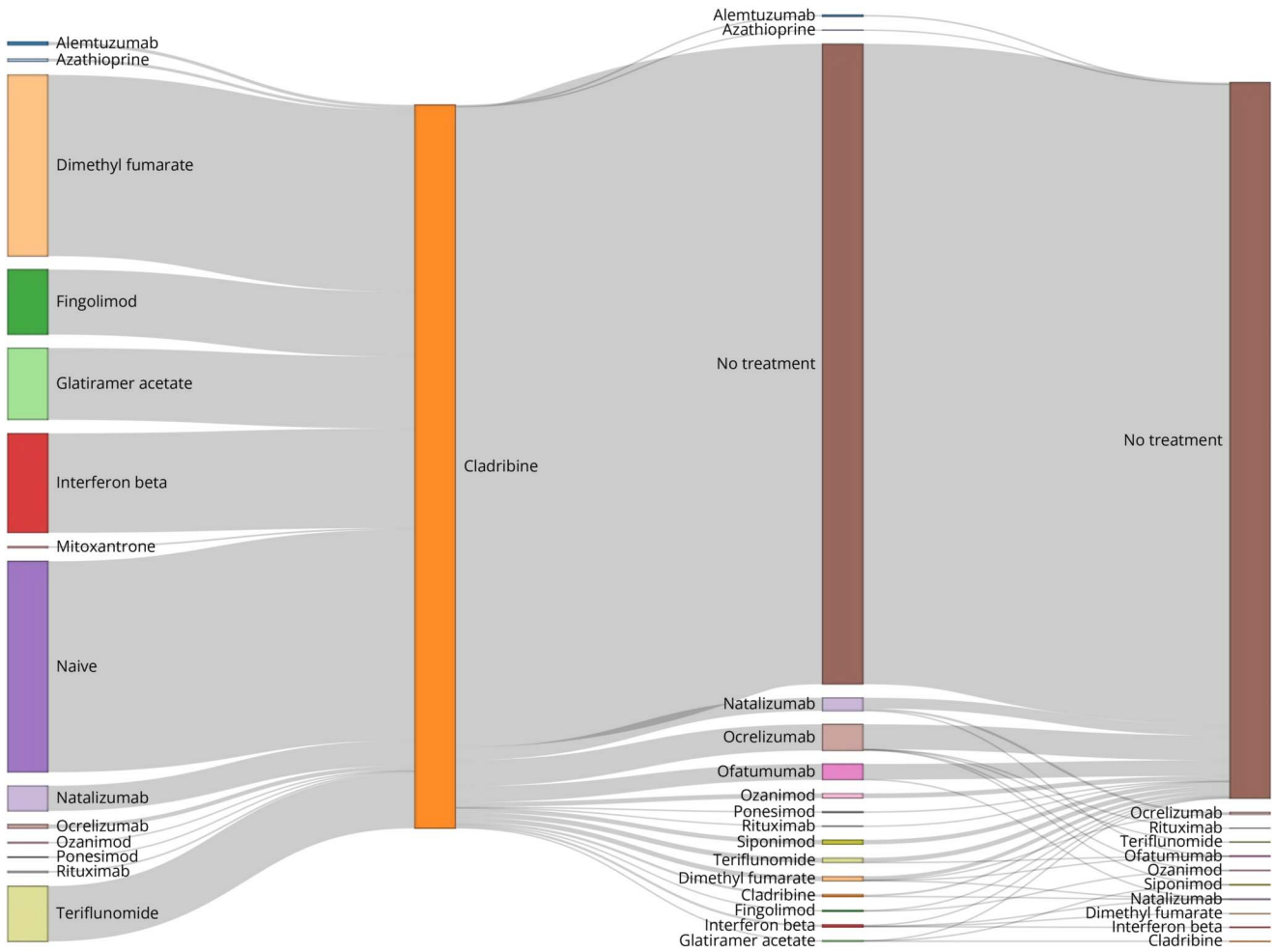
Table 2 Last Disease-Modifying Treatment (DMT) Before Cladribine Initiation in the Overall Cohort

DMT before cladribine	N = 2,329
Interferon-beta products	320
Teriflunomide	178
Azathioprine	9
Glatiramer acetate	231
Dimethyl fumarate	583
Fingolimod	209
Alemtuzumab	10
Rituximab	5
Mitoxantrone	5
Natalizumab	81
Ocrelizumab	13
Ponesimod	2
Ozanimod	4
Naïve	679

Table 3 Disease-Modifying Treatments (DMTs) After Cladribine Treatment

DMT after cladribine	N. first DMT after cladribine treatment	N. second DMT after cladribine treatment
Teriflunomide	16	1
Azathioprine	1	
Glatiramer acetate	3	
Fingolimod	3	
Ofatumumab	51	3
Alemtuzumab	5	
Rituximab	1	1
Cladribine	7	1
Siponimod	14	2
Ocrelizumab	84	8
Interferon-beta	7	1
Ponesimod	3	
Dimethyl fumarate	15	1
Natalizumab	42	4
Ozanimod	15	2
No DMT	2,062	2,305

Figure 1 Sankey Plot of Treatment Pathways



in ARR from 0.67 (0.57–0.69) to 0.18 (0.13–0.24) after treatment (Figure 2).

In the subcohort of 1,488 patients who completed 2 cycles of cladribine, ARR decreased ($p < 0.0001$) from 1.05 (95% CI 0.98–1.13) in the 2 years preceding cladribine start to 0.12 (95% CI 0.10–0.14) during the 2 years after. Regardless of age at treatment initiation or previous DMT efficacy profile, all analyses stratified by age and previous treatment confirmed the significant decrease in ARR ($p < 0.0001$). Considering the age cutoff of 50 years, pretreatment ARR of 0.62 (0.50–0.77) in patients who started treatment at least at 50 years of age converted to a post-treatment ARR of 0.06 (0.04–0.11); pretreatment ARR of 1.12 (1.04–1.20) in patients who began treatment at an age younger than 50 years changed to a post-treatment ARR of 0.13 (0.11–0.15). In naïve patients, the pretreatment ARR was 1.92 (1.74–2.12) and it dropped to 0.13 (0.09–0.18) after the 2 cycles of cladribine. In patients treated with ME DMTs before cladribine, ARR decreased from 0.77 (0.70–0.85) to 0.09 (0.07–0.11) after the 2 cycles. After receiving full cladribine treatment, the ARR in patients treated with HE DMTs before cladribine went from 0.75 (0.64–0.90) to 0.20 (0.15–0.28).

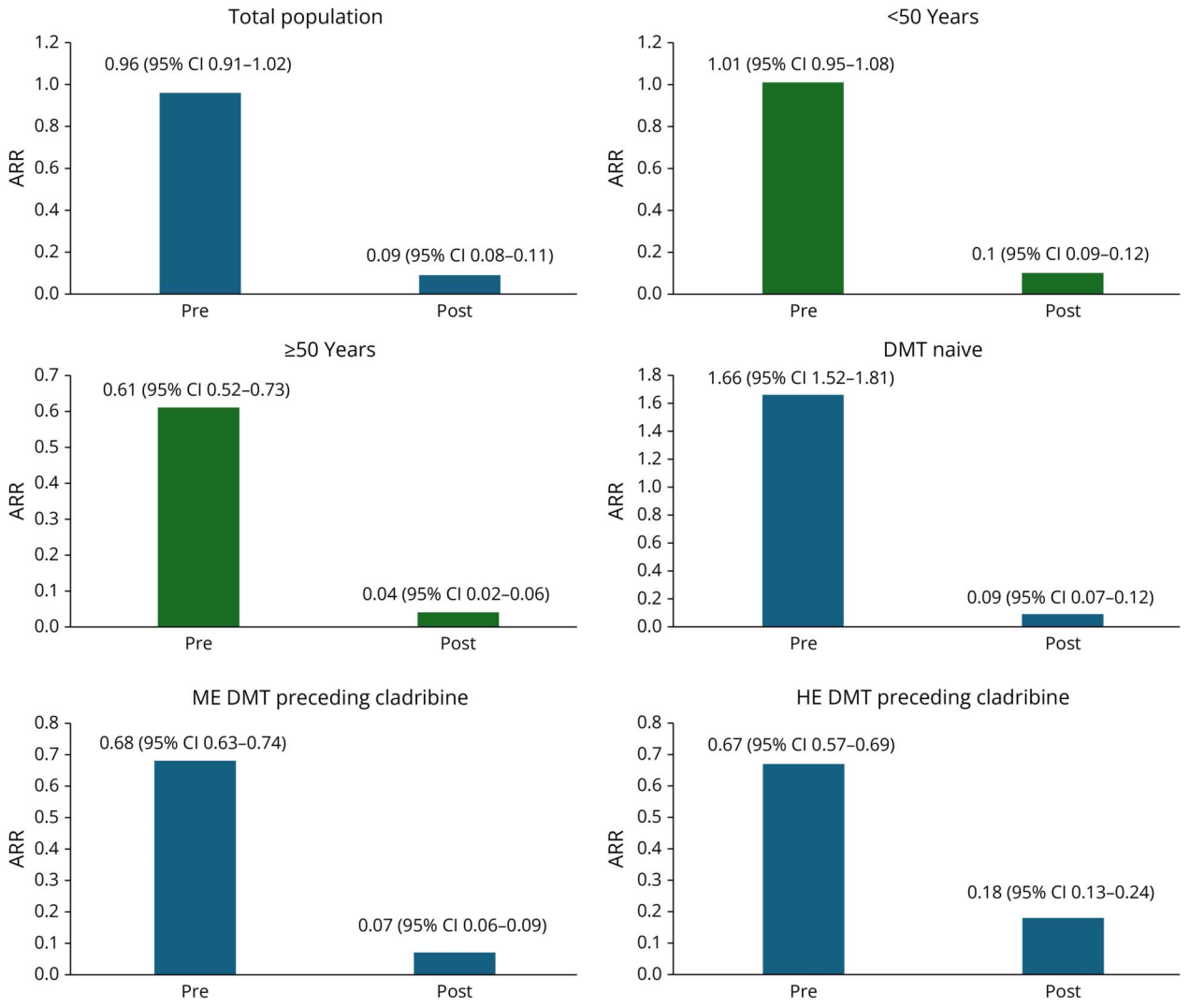
PIRA Evaluation

PIRA events were calculated in a subcohort of 978 patients, all treated with 2 cycles of cladribine. The median follow-up was 6.71 years (0.32–28.29).

Considering the overall population, 133 PIRA events in 93 patients were reported during the noncladribine treatment period and 54 in 35 patients during cladribine therapy (HR 0.711, 95% CI 0.531–0.952, $p = 0.0219$) (Figures 3 and 4).

In the group starting therapy at an age younger than 50 years (865 patients), 96 PIRA events were reported during the noncladribine treatment period and 42 during cladribine therapy (HR 0.679, 95% CI 0.489–0.943, $p = 0.0207$); in the group starting therapy after 50 years of age (113 patients), 37 PIRA events were reported during the noncladribine treatment period and 12 during cladribine therapy (HR 1.36, 95% CI 0.657–2.833, $p = 0.405$). The p value of cladribine treatment-

Figure 2 ARR in the Entire Cohort and in the Subgroup Analysis



ARR = annualized relapse rate; DMT = disease-modifying treatment; HE = highly effective; ME = moderately effective.

by-age class interaction term corresponded to 0.0858. In addition, a significant p value of 0.000143 for the treatment-by-age interaction term indicated a more pronounced efficacy in reducing PIRA events in younger patients.

PIRA events were also evaluated by stratifying the cohort according to the preceding DMT. Therefore, the analysis considered naïve subjects (238 patients) and patients previously treated with ME or HE DMTs (560 and 180 patients, respectively). In naïve patients, 4 PIRA events were reported before the start of treatment and 11 during cladribine therapy (HR 0.61, 95% CI 0.191–1.949, p = 0.405). In patients first treated with ME DMTs, 79 PIRA events were reported before treatment initiation and 32 during cladribine therapy (HR 0.903, 95% CI 0.627–1.299, p = 0.582). In patients treated first with HE DMTs, 50 PIRA events were reported before treatment initiation and 11 during cladribine therapy (HR 0.465, 95% CI 0.240–0.901, p = 0.0233). The p value of cladribine treatment-by-previous treatment interaction corresponded to 0.612, thus indicating no evidence of a differential efficacy among groups with different previous treatments. Kaplan-Meier curves showing the proportion of patients with event-free survival defined as PIRA-free probability are illustrated in Figure 4.

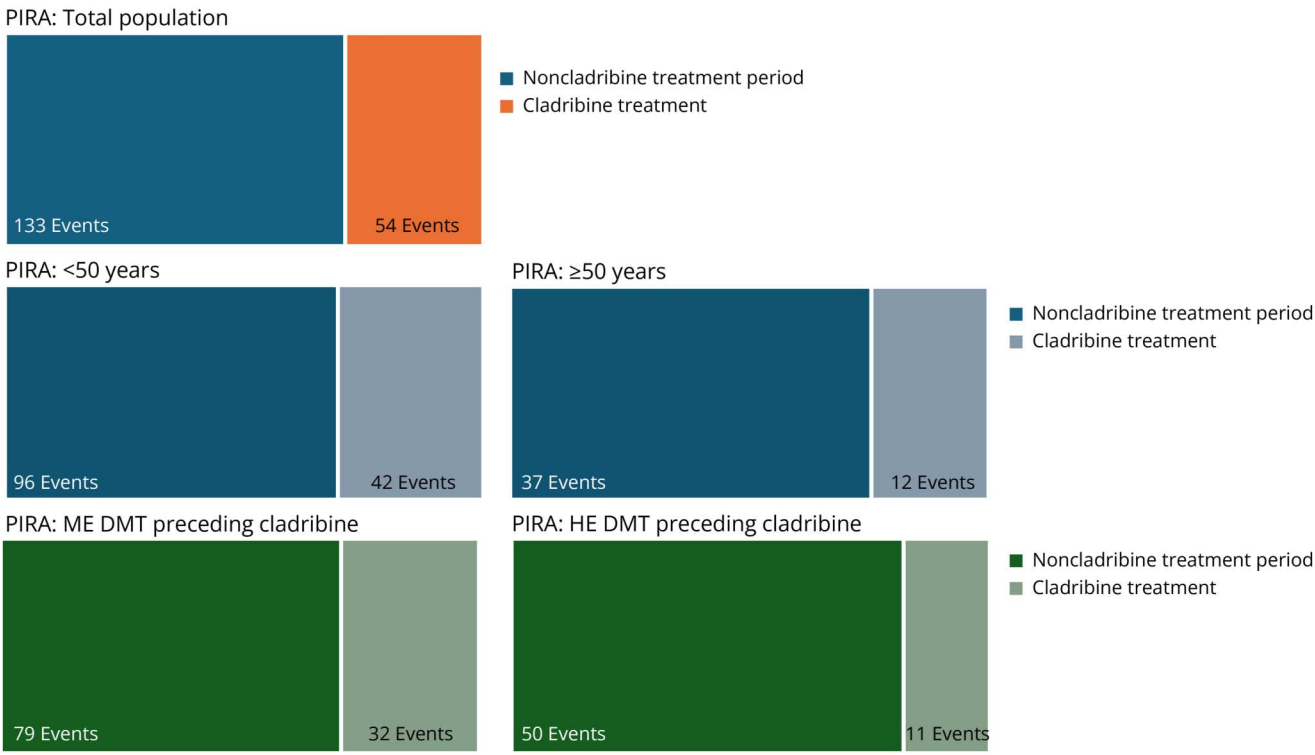
Classification of Evidence

This study provides Class IV evidence that for patients with RMS, cladribine treatment is associated with a reduction in ARR and PIRA events.

Discussion

In this multicenter, observational, retrospective cohort study based on RISM data, we assessed the effectiveness profile of cladribine, evaluating the effect on ARR and the impact on PIRA events. For patients with RMS, both naïve and switchers, as well as younger and older patients, the treatment with cladribine was successful.

Figure 3 Proportion of PIRA Events in the Entire Cohort and in the Subgroup Analysis



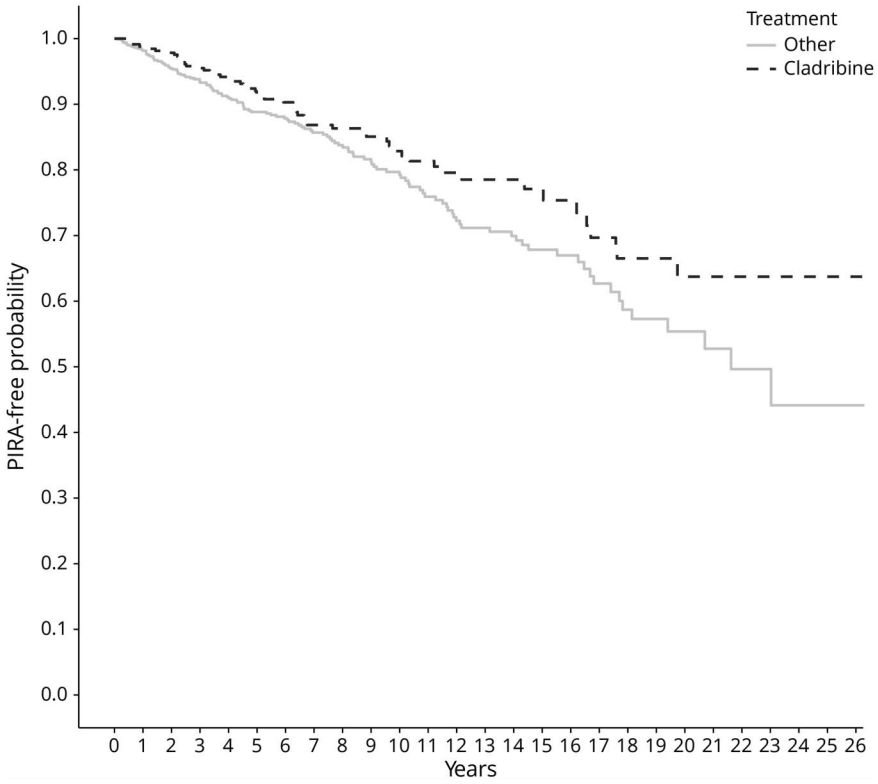
DMT = disease-modifying treatment; HE = highly effective; ME = moderately effective; PIRA = progression independent of relapse activity.

Our results are in line with the growing amount of evidence about cladribine effectiveness published in the past few years. A recent monocentric real-world study on 114 patients with relapsing remitting MS treated with cladribine proved a reduction in relapses and MRI activity, along with a stabilization of disability, over the long term, with 74.9% of patients achieving no-evidence-of-disease-activity-3 (NEDA-3) status at 24 months.[22] In the MSBase Registry, clinical outcomes of dimethyl fumarate, teriflunomide, cladribine, and fingolimod were compared, proving that cladribine cohorts had significantly longer time to treatment discontinuation, longer time to first relapse, and lower ARR.[23] In the CLARITY study, cladribine tablets significantly decreased the probability of 3-month and 6-month confirmed disability worsening and the ARR by 58% when compared with placebo ($p < 0.001$).[7] Another study demonstrated that, compared with the ARR of 0.67 (95% CI [0.56–0.79]) in the year before initiation of cladribine, ARR was reduced to 0.11 (95% CI [0.08–0.15]) in years 0–2 after 3-month re-baseline with cladribine (84.8% reduction). The analysis stratified by previous therapy confirmed a significant ARR reduction in all subgroups, although less pronounced in cladribine-treated patients switching from HE DMTs.[24] After a median follow-up period of 19 months, the mean ARR in a Finnish nationwide register study including 179 patients was found to be 0.1, as opposed to 1.0 before the start of cladribine therapy.[25] A reduction in the ARR at the 12-month follow-up after cladribine completion compared with the year before starting therapy (0.07 ± 0.25 vs 0.82 ± 0.80, $p < 0.001$) was also observed in a retrospective, multicenter Italian study.[26] Similar trends were observed in our cohort, regardless of age at treatment start and previous DMT efficacy profile.

PIRA is now considered the main driver of disability accumulation in MS.[14,15] Therefore, it is crucial to collect real-world evidence to understand whether the pathogenetic mechanisms sustaining PIRA can be modified by currently approved DMTs. Our study provides novel insights into the effect of cladribine on PIRA events, stratifying patients in different cohorts based on age and treatment history. We found a reduction in PIRA events, comparing the observation period before and after cladribine therapy, in all subcohorts of patients. The exception is the group of patients naïve to treatment. In this specific subgroup, it was not possible to see an effect of cladribine on the PIRA risk just because the model we used compared the periods before and after the treatment start. Because cladribine in naïve patients is used with a short delay after the diagnosis, there were more chances to detect a disability worsening independent of relapse activity after the treatment start than before. A longer follow-up is required to detect an effect on PIRA risk in naïve patients.

IRTs may be most beneficial when used early in the disease course. Zanetta et al. reported that cladribine was more effective in first-line therapy switchers or naïve patients.[22] Another study analyzing data from 243 patients with MS

Figure 4 Kaplan-Meier Curves of the Proportion of Patients With Event-Free Survival Defined as PIRA-Free Probability



The figure shows the Kaplan-Meier curves reporting the proportion of patients without PIRA events (PIRA-free probability) stratified based on the time-dependent exposure to cladribine over the entire follow-up period. PIRA = progression independent of relapse activity.

followed at 8 Italian MS centers showed that patients with a higher number of previous treatments had a lower probability of retaining NEDA-3 status and an increased risk of clinical relapses.[27] On the contrary, a recent review considering the changing demographic background of RMS and the challenges associated with aging people with RMS pointed out that long-term follow-up of RMS populations in randomized trials alongside real-world evidence suggests that the effectiveness of cladribine in suppressing MS disease activity is similar in older and younger age groups, with a solid safety profile.[28] In our cohort, cladribine resulted effective in both younger and older patients.

Research questions increase in tandem with real-world challenges: there have been an increasing number of questions in recent years concerning the continuation of therapy after the completion of 2 cladribine courses. Our results are consistent with other reports based on real-life data, confirming that ocrelizumab and natalizumab are the primary choices after cladribine therapy.[26,29] A recent expert opinion identified 5 patient categories classified by clinical and MRI activity and biomarker evaluation that could benefit from treatment with cladribine tablets beyond year 4, underlining that patients who do not achieve NEDA-3 status should be candidates for retreatment with cladribine tablets.[30] In our register, we identified 8 patients treated with an additional cycle. This number may still be minimal because of the rules of prescription and refundability of the drug currently present in Italy.

A few limitations of our study should be taken into account. As with previous retrospective observational studies from the IMSR, incomplete or inaccurate data entered in the register must be acknowledged. In defining PIRA events, we considered solely the EDSS score because we could not incorporate MRI data because of the lack of a systematic acquisition of neuroimaging data in the RISM database. Because MRI biomarkers are a key element in determining the disease burden and constitute a critical prognostic factor, especially when assessing disease activity on therapy, this consideration must be emphasized. A longer follow-up will provide a deeper understanding of the sustained effectiveness of cladribine, especially on PIRA events. However, our study used the large and validated database of RISM to assess the effectiveness profile of cladribine and therapeutic choices after treatment completion.

In conclusion, results from our cohort extracted from the large and validated RISM database highlighted the effectiveness profile of cladribine in suppressing relapse activity and in reducing the occurrence of PIRA events, thus addressing neuroinflammation and neurodegeneration, the 2 faces of MS disability accumulation. A longer follow-up will be essential to validate these findings and to better characterize treatment patterns after the completion of both cladribine cycles.

Acknowledgment

The authors thank the Research Assistants of RISM (Italian MS Foundation - FISM): Beatrice Biolzi, Camilla Borgo,

Antonella Carta, Paola Crida, Daniele Dell'Anna, Marco Delogu, Daniele Di Giulio Cesare, Sonia di Lemme, Chiara Di Tillio, Teresa Fonsdituri, Ilaria Maietta, Agata Marchese, Martina Marciano, Silvia Marinetto, Federica Martini, Chiara Monetti, Cristiana Morano, Ornella Moreggia, Silvia Perugini, Giovanna Ramona Piredda, Chiara Raimondi, Antonino Rallo, Monica Romoli, Ilaria Rossi, Valentina Tallarico, Stefania Treccarichi, Eliana Zaccone. The Research Assistants of RISM contributed to data collection.

Author Contributions

T. Guerra: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Copetti: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. C. Zanetta: drafting/revision of the manuscript for content, including medical writing for content. F. Patti: drafting/revision of the manuscript for content, including medical writing for content. C.G. Chisari: drafting/revision of the manuscript for content, including medical writing for content. E. Barbuti: drafting/revision of the manuscript for content, including medical writing for content. E. Portaccio: drafting/revision of the manuscript for content, including medical writing for content. M. Foschi: drafting/revision of the manuscript for content, including medical writing for content. A. Conte: drafting/revision of the manuscript for content, including medical writing for content. D. Ferraro: drafting/revision of the manuscript for content, including medical writing for content. E.E. Cocco: drafting/revision of the manuscript for content, including medical writing for content. R. Fantozzi: drafting/revision of the manuscript for content, including medical writing for content. G.T. Maniscalco: drafting/revision of the manuscript for content, including medical writing for content. G. Salemi: drafting/revision of the manuscript for content, including medical writing for content. C. Tortorella: drafting/revision of the manuscript for content, including medical writing for content. D. Paolicelli: drafting/revision of the manuscript for content, including medical writing for content. M. Filippi: drafting/revision of the manuscript for content, including medical writing for content. M.P. Amato: drafting/revision of the manuscript for content, including medical writing for content. M. Trojano: drafting/revision of the manuscript for content, including medical writing for content. P. Iaffaldano: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no conflicts of interest with respect to the contents of the current study, but note that the patients in the study were treated with a number of disease-modifying drugs and that authors have received advisory board, membership, speakers honoraria, travel support, research grants, consulting fees, or clinical trial support from the manufacturers of those drugs, including Actelion, Allergan, Almirall, Alexion, Bayer Schering, Biogen, Celgene, Excemed, Genzyme, Forward Pharma, Ipsen, Medday, Merck, Mylan, Novartis, Sanofi, Roche, Teva, and their local affiliates. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology® Neuroimmunology & Neuroinflammation* October 29, 2024. Accepted in final form April 25, 2025. Submitted and externally peer reviewed. The handling editor was Anne-Katrin Pröbstel, MD.

References

1. Giovannoni G, Mathews J. Cladribine tablets for relapsing-remitting multiple sclerosis: a clinician's review. *Neurol Ther*. 2022;11(2):571-595. doi:10.1007/s40120-022-00339-7
2. Comi G, Dalla Costa G, Moiola L. Newly approved agents for relapsing remitting multiple sclerosis: how real-world evidence compares with randomized clinical trials? *Expert Rev Neurother*. 2021;21(1):21-34. doi:10.1080/14737175.2021.1829478
3. Filippi M, Amato MP, Centonze D, et al. Early use of high-efficacy disease-modifying therapies makes the difference in people with multiple sclerosis: an expert opinion. *J Neurol*. 2022;269(10):5382-5394. doi:10.1007/s00415-022-11193-w
4. Rammohan K, Coyle PK, Sylvester E, et al. The development of cladribine tablets for the treatment of multiple sclerosis: a comprehensive review. *Drugs*. 2020;80(18):1901-1928. doi:10.1007/s40265-020-01422-9
5. Jacobs BM, Ammoscato F, Giovannoni G, Baker D, Schmierer K. Cladribine: mechanisms and mysteries in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2018;89(12):1266-1271. doi:10.1136/jnnp-2017-317411
6. Brochet B, Solari A, Lechner-Scott J, et al. Improvements in quality of life over 2 years with cladribine tablets in people with relapsing multiple sclerosis: the CLARIFY-MS study. *Mult Scler*. 2023;29(14):1808-1818. doi:10.1177/13524585231205962
7. Giovannoni G, Comi G, Cook S, et al.; CLARITY Study Group. A placebo controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):416-426. doi:10.1056/NEJMoa0902533
8. Giovannoni G, Soelberg Sorensen P, Cook S, et al. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: results from the randomized extension trial of the CLARITY study. *Mult Scler*. 2018;24(12):1594-1604. doi:10.1177/1352458517727603
9. Giovannoni G, Boyko A, Correale J, et al. Long-term follow-up of patients with relapsing multiple sclerosis from the CLARITY/CLARITY Extension cohort of CLASSIC-MS: an ambispective study. *Mult Scler*. 2023;29(6):719-730. doi:10.1177/13524585231161494
10. Patti F, Visconti A, Capacchione A, Roy S, Trojano M, CLARINET-MS Study Group. Long-term effectiveness in patients previously treated with cladribine tablets: a real-world analysis of the Italian multiple sclerosis registry (CLARINET-MS). *Ther Adv Neurol Disord*. 2020;13:1756286420922685. doi:10.1177/1756286420922685
11. Lizak N, Hodgkinson S, Butler E, et al. Real-world effectiveness of cladribine for Australian patients with multiple sclerosis: an MSBase registry substudy. *Mult Scler*. 2021;27(3):465-474. doi:10.1177/1352458520921087
12. Song Y, Wang Y, Wong SL, Yang D, Sundar M, Tundia N. Real-world treatment patterns and effectiveness of cladribine tablets in patients with relapsing forms of multiple sclerosis in the United States. *Mult Scler Relat Disord*. 2023;79:105052. doi:10.1016/j.msard.2023.105052
13. de Stefano N, Barkhof F, Montalban X, et al. Early reduction of MRI activity during 6 months of treatment with cladribine tablets for highly active relapsing multiple sclerosis: MAGNIFY-MS. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(4):e1187. doi:10.1212/nxi.0000000000001187
14. Iaffaldano P, Portaccio E, Lucisano G, et al. Multiple sclerosis progression and relapse activity in children. *JAMA Neurol*. 2024;81(1):50–58. doi:10.1001/jamaneurol.2023.5461
15. Portaccio E, Magyari M, Havrdova EK, et al. Multiple sclerosis: emerging epidemiological trends and redefining the clinical course. *Lancet Reg Health Eur*. 2024;44:100977. doi:10.1016/j.lanepe.2024.100977
16. Trojano M, Kalincik T, Iaffaldano P, Amato MP. Interrogating large multiple sclerosis registries and databases: what information can be gained? *Curr Opin Neurol*. 2022;35(3):271-277. doi:10.1097/WCO.0000000000001057
17. Trojano M, Bergamaschi R, Amato MP, et al. The Italian multiple sclerosis register. *Neurol Sci*. 2019;40(1):155–165. doi:10.1007/s10072-019-03772-z
18. Mosconi P, Guerra T, Paletta P, et al. Data monitoring roadmap. The experience of the Italian multiple sclerosis and related disorders register. *Neurol Sci*. 2023;44(11):4001-4011. doi:10.1007/s10072-023-06876-9
19. Filippi M, Danesi R, Derfuss T, et al. Early and unrestricted access to high-efficacy disease-modifying therapies: a consensus to optimize benefits for people

living with multiple sclerosis. *J Neurol*. 2022;269(3):1670-1677. doi:10.1007/s00415-021-10836-8
20. Akaishi T, Ishii T, Aoki M, Nakashima I. Calculating and comparing the annualized relapse rate and estimating the confidence interval in relapsing neurological diseases. *Front Neurol*. 2022;13:875456. doi:10.3389/fneur.2022.875456
21. Sharrad D, Chugh P, Slee M, Bacchi S. Defining progression independent of relapse activity (PIRA) in adult patients with relapsing multiple sclerosis: a systematic review. *Mult Scler Relat Disord*. 2023;78:104899. doi:10.1016/j.msard.2023.104899
22. Zanetta C, Rocca MA, Meani A, et al. Effectiveness and safety profile of cladribine in an Italian real-life cohort of relapsing-remitting multiple sclerosis patients: a monocentric longitudinal observational study. *J Neurol*. 2023;270(7):3565-3566.
23. Spelman T, Ozakbas S, Alroughani R, et al. Comparative effectiveness of cladribine tablets versus other oral disease-modifying treatments for multiple sclerosis: results from MSBase registry. *Mult Scler*. 2023;29(2):221-235. doi:10.1177/13524585221137502
24. Sorensen PS, Pontieri L, Joensen H, et al. Real-world experience of cladribine treatment in relapsing-remitting multiple sclerosis: a Danish nationwide study. *Mult Scler Relat Disord*. 2023;70:104491. doi:10.1016/j.msard.2022.104491
25. Rauma I, Viitala M, Kuusisto H, et al. Finnish multiple sclerosis patients treated with cladribine tablets: a nationwide registry study. *Mult Scler Relat Disord*. 2022;61:103755. doi:10.1016/j.msard.2022.103755
26. Schiavetti I, Signori A, Albanese A, et al. Therapeutic choices and disease activity after 2 years of treatment with cladribine: an Italian multicenter study (CladStop). *Eur J Neurol*. 2024;31(6):e16250. doi:10.1111/ene.16250
27. Petracca M, Ruggieri S, Barbuti E, et al. Predictors of cladribine effectiveness and safety in multiple sclerosis: a real-world, multicenter, 2-year follow-up study. *Neurol Ther*. 2022;11(3):1193-1208. doi:10.1007/s40120-022-00364-6
28. de Seze J, Dive D, Ayrignac X, et al. Narrative review on the use of cladribine tablets as exit therapy for stable elderly patients with multiple sclerosis. *Neurol Ther*. 2024;13(3):519-533. doi:10.1007/s40120-024-00603-y
29. Brownlee W, Amin A, Ashton L, Herbert A. Real-world use of cladribine tablets (completion rates and treatment persistence) in patients with multiple sclerosis in England: the CLARENCE study. *Mult Scler Relat Disord*. 2023;79:104951. doi:10.1016/j.msard.2023.104951
30. Centonze D, Amato MP, Brescia Morra V, et al. Multiple sclerosis patients treated with cladribine tablets: expert opinion on practical management after year 4. *Ther Adv Neurol Disord*. 2023;16:17562864231183221. doi:10.1177/17562864231183221