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Cladribine tablets for highly active relapsing-remitting multiple sclerosis in Poland: a real-world, multi-centre, retrospective, cohort study during the COVID-19 pandemic

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ABSTRACT

Introduction. Treatment with cladribine tablets is indicated in highly active relapsing-remitting multiple sclerosis (RRMS). Cladribine tablets proved safe and effective in the pivotal CLARITY trial, but that trial included primarily treatment-naïve patients. In clinical practice however, cladribine tablets are often given to patients who have failed other treatments. Therefore, this study investigated the real-world safety and efficacy of cladribine tablets.

Material and methods. We gathered data from nine MS clinical centres across Poland for patients with RRMS who started treatment with cladribine tablets from December 2019 to June 2022.

Results. We enrolled 140 patients, with follow-up data available for 136 in year 1 and for 66 in year 2. At baseline, the mean age was 35.6 years, mean disease duration was 7.3 years, median EDSS score was 2.5, and 94% of patients were treatment-experienced. Thirty-nine patients (27.9%) had undergone COVID-19, and 94 (67.1%) were vaccinated against COVID-19. The annualised relapse rate (ARR) decreased from 1.49 at baseline to 0.33 in year 1 ($p < 0.001$) and to 0.25 in year 2 ($p < 0.001$). The percentage of relapse-free patients increased from 11.5% at baseline to 70.2% in year 1 and 82.1% in year 2. The percentage of patients with active lesions decreased from 91.4% at baseline to 36.2% in year 1 and 18.2% in year 2. EDSS score remained stable or improved in 83.7% of patients in year 1 and 89.6% in year 2. No evidence of disease activity (NEDA-3) was achieved in 42.7% of patients in year 1 and 66.7% in year 2. Only one patient (0.72%) had grade 4 lymphopenia and 21 (15.1%) had grade 3 lymphopenia. *Varicella zoster* virus infections occurred in three patients. Eight patients discontinued treatment with cladribine: five due to inefficacy, one due to lymphopenia, and two due to a personal decision.

Conclusions. Cladribine tablets proved safe and effective in a real-world cohort of treatment-experienced patients. However, the efficacy measures improved to a lesser extent in our cohort than in the pivotal clinical trial, which is probably due to a higher proportion of treatment-experienced patients in our cohort.

Key words: cladribine, relapsing-remitting multiple sclerosis, safety, efficacy, COVID-19

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Introduction

Multiple sclerosis (MS) is a chronic and progressive neurological disease characterised by recurrent episodes of inflammatory demyelination of the brain and spinal cord [1, 2]. Cladribine is a potent anti-inflammatory agent to treat relapsing-remitting MS (RRMS). The drug selectively targets lymphocytes, depleting primarily CD19+ B cells, with a small reduction in CD4+ or CD8+ T-cells and CD16+/CD56+ natural killer cells [3–5]. Cladribine depletes lymphocytes via apoptosis rather than cell lysis, which is associated with a favourable safety profile during dosing. Cladribine is given in two courses 12 months apart, and leads to long-lasting disease control without the need for chronic immunosuppression and with minimal monitoring requirements [6]. This treatment regimen with cladribine tablets was particularly advantageous during the COVID-19 pandemic, often requiring self-isolation at home.

In the pivotal phase III trial among primarily treatment-naïve patients, cladribine tablets significantly reduced the annualised relapse rate, risk of disability progression, lesion activity on neuroimaging, and brain atrophy [7]. In Poland, cladribine tablets were approved for highly active RRMS in 2017 when the drug was licensed in the European Union [6]. However, the reimbursement criteria in Poland require evidence of a more active disease than is specified in the drug's label [6, 8].

Six years after the marketing authorisation of cladribine tablets, the data on its safety and efficacy in a real-world setting is limited. Our study aimed to examine the real-world efficacy and safety of cladribine tablets given as part of the reimbursement scheme in Poland, mostly to patients who had failed other disease-modifying therapies (DMTs).

Clinical rationale for the study

Treatment with cladribine tablets proved safe and effective in the CLARITY trial. However, that trial was carried out when few DMTs were available to patients with RRMS. Consequently, the CLARITY trial enrolled primarily treatment-naïve patients. Recently, the treatment landscape has changed considerably, with more than a dozen DMTs now available. Cladribine tables are now often given to patients who have failed previous treatments, including other high-efficacy DMTs. Therefore, post-marketing studies are needed to investigate the real-world safety and efficacy of cladribine tablets.

Material and methods

This retrospective observational study was carried out in nine MS clinical centres across Poland in a cohort of all patients with RRMS who started treatment with cladribine tablets from December 2019 to June 2022. One treatment course consisted of two cycles. All diagnoses complied with the 2017 revisions of the McDonald criteria [9]. The study was approved by the ethics committee of the Polish Military Chamber of Physicians (approval no. 235/22).

We gathered the following data: demographics; disease duration; prior DMTs; the number of relapses in the 12 months before cladribine initiation and 12 and 24 months after treatment initiation; EDSS scores at cladribine initiation and 12 and 24 months later; the reason for discontinuing previous DMTs; adverse reactions; history of COVID-19 infection and SARS-CoV-2 vaccination; and lymphocyte counts before cladribine initiation and at two, six, 12, 14, and 18 months.

Active MRI lesions were defined as Gd(+) or new/enlarging T2 lesions. No evidence of disease activity (NEDA-3) was defined as the absence of clinical relapses, disability progression, and active MRI lesions [10]. The annualised relapse rates (ARRs) with 95% confidence intervals (CI) were calculated with a negative binomial regression model for the 12 months before the first course, 12 months between the two courses, and 12 months after the second course. In accordance with previous reports [11], changes in EDSS scores were classified as an improvement or worsening as follows: among patients with baseline EDSS of 0 — a change of at least 1.5 points; among patients with baseline EDSS of 0.5 to 4.5 — a change of at least 1 point; and among patients with baseline EDSS ≥ 5 — a change of at least 0.5 points. EDSS changes that did not meet the criteria for an improvement or worsening were classified as stable EDSS. Lymphopenia grades were defined as follows: grade I (< 1.0–0.8 × 10^9/L); grade II (< 0.8–0.5 × 10^9/L); grade III (< 0.5–0.2 × 10^9/L); and grade IV (< 0.2 × 10^9/L) [12]. We assessed the frequency of lymphopenia among patients who had lymphocyte counts measured two months after the first treatment cycle or later, taking into account the lowest value of the lymphocyte count for each patient.

Descriptive data was presented as means ± standard deviations (SD) or medians and interquartile ranges (IQR). A Wilcoxon test was used to compare the ARR and EDSS at year 1 and year 2 with the ARR at baseline. A p-value < 0.05 was considered statistically significant. All analyses were completed in the R software (version 4.1.3).

Results

Cohort description

In total, 140 patients who started treatment with cladribine tablets were enrolled in the study: four patients completed only one treatment week and were excluded from the efficacy analysis; 70 patients received one course (1.75 mg/kg), and 66 received two courses (3.5 mg/kg). Thus, follow-up data was available for 136 patients in year 1 and for 66 patients in year 2 (Fig. 1).

Of the 140 patients, 109 (77.9%) were women, the mean (SD) age was 35.6 (11.0) years, the mean disease duration was 7.3 (5.2) years, and the median (IQR) EDSS at baseline was 2.5 (1.5, 3.5).

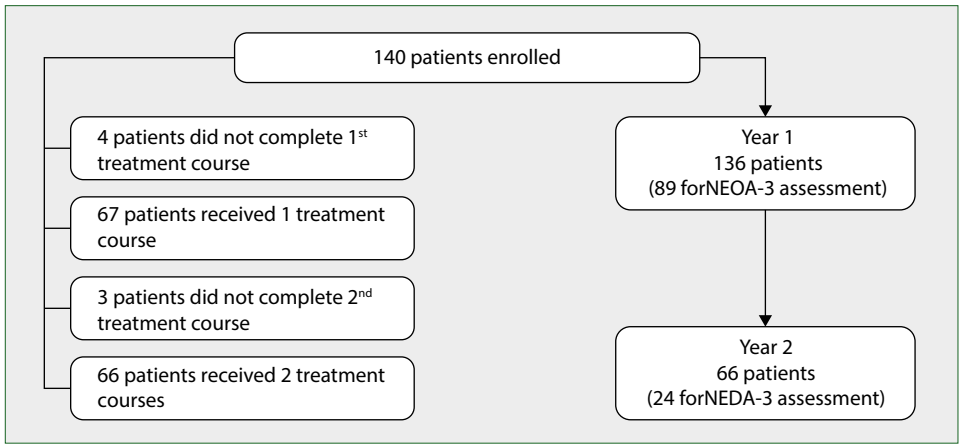

Figure 1. Flow diagram showing disposition of patients enrolled to study

Before cladribine tablets, 131 (93.6%) patients had previously received at least one DMT, whereas only eight patients were treatment-naïve (all had rapidly evolving severe MS). Most patients were switched from dimethyl fumarate (43.8%), fingolimod (17.7%), or natalizumab (10.8%). Inefficacy was the most frequent reason for discontinuing previous DMTs (86.3% of patients). Thirty-nine patients (27.9%) had undergone COVID-19, and 94 (67.1%) had been vaccinated against COVID-19 during the study. Table 1 sets out the baseline characteristics in detail.

Efficacy

The ARR decreased from 1.49 (95% CI: 1.30–1.70) at baseline to 0.33 (0.23–0.46) at year 1 ($p < 0.001$) and to 0.25 (0.11–0.48) at year 2 ($p < 0.001$, Fig. 2A). The percentage of relapse-free patients increased from 11.5% at baseline to 70.2% in year 1 and 82.1% in year 2 (Fig. 2B). The percentage of patients with active MRI lesions decreased from 91.4% at baseline to 36.2% in year 1 and 18.2% in year 2 (Fig. 2C). EDSS remained stable or improved in 83.7% of patients in year 1 and 89.6% in year 2 (Fig. 2D). Compared to baseline, the median EDSS score did not change significantly at year 1 [2.75 (1.50, 4.00), $p = 0.643$] and year 2 [3.00 (2.00, 4.00) $p = 0.135$]. Among patients with sufficient data (see Fig. 1), NEDA-3 was achieved in 42.7% of patients in year 1 and 66.7% in year 2 (percentages of patients with the full set of data needed for NEDA-3 assessment, Fig. 2E). Table 2 sets out the detailed characteristics by NEDA-3 status.

Safety

All patients had a lymphocyte count of at least 800/μL before the start of treatment with cladribine tablets [median 1.56 (1.25, 2.00)]. The median lymphocyte count was 0.88 (0.70, 1.00) at two months, 0.94 (0.80, 1.16) at six months, 1.11 (0.90, 1.45) at 12 months, 0.77 (0.56, 1.00) at 14 months, and 0.86 (0.68, 1.15) at 18 months (see Fig. 3). Only one patient (0.72%) had grade 4 lymphopenia, 21 (15.1%) had grade 3 lymphopenia, 52 (37.4%) had grade 2 lymphopenia,

Table 1. Baseline characteristics of study patients

Characteristic	
Sex (female); n (%)	109 (77.9)
Age (years); mean (SD)	35.6 (11.0)
Disease duration (years); mean (SD)	7.3 (5.2)
Time from last DMT to cladribine (months); mean (SD)	4.3 (9.5)
Number of previous DMTs; n (%)	
0*	8 (5.8)
1–2	94 (67.2)
≥ 3	37 (26.4)
EDSS; median (IQR)	2.5 (1.5, 3.5)
ARR; mean (SD)	1.49 (0.88)
Patients with active MRI changes; n (%**)	127 (91.4)
Lymphocyte count (cells/μL); median (IQR)	1,560 (1,250, 2,000)
Patients who underwent COVID-19; n (%)	39 (27.9)
Patients vaccinated against COVID-19; n (%)	94 (67.1)
DMT; n (%***)	
Dimethyl fumarate	57 (43.8)
Fingolimod	23 (17.7)
Natalizumab	14 (10.8)
Teriflunomide	12 (9.2)
Glatiramer acetate	10 (7.7)
IFNβ-1a	6 (4.6)
IFNβ-1b	5 (3.8)
Ocrelizumab	2 (1.5)
Alemtuzumab	1 (0.8)
Reason for last DMT discontinuation; n (%)	
switch from 1st line DMT for inefficacy****	89 (68.5)
switch from 2nd line DMT for inefficacy	23 (17.7)
switch from 2nd line DMT for adverse events	8 (6.1)
switch from 2nd line DMT for high titre of anti-JCV antibodies	8 (6.1)
planned pregnancy	2 (1.5)

*All naive patients (not previously treated with DMT) had rapidly evolving severe multiple sclerosis
**Percentage of patients with available MRI data (N = 139)
***Percentage of patients with available data on previous DMT (N = 130)
****Second-line treatments include fingolimod, natalizumab, ocrelizumab, and alemtuzumab. Other treatments are considered first-line
ARR — annualised relapse rate; COVID-19 — coronavirus disease 19; DMF — dimethyl fumarate; DMT — disease-modifying therapy; EDSS — Expanded Disability Status Scale; IFNβ — interferon β; IQR — interquartile range; JCV — John Cunningham virus; SD — standard deviation

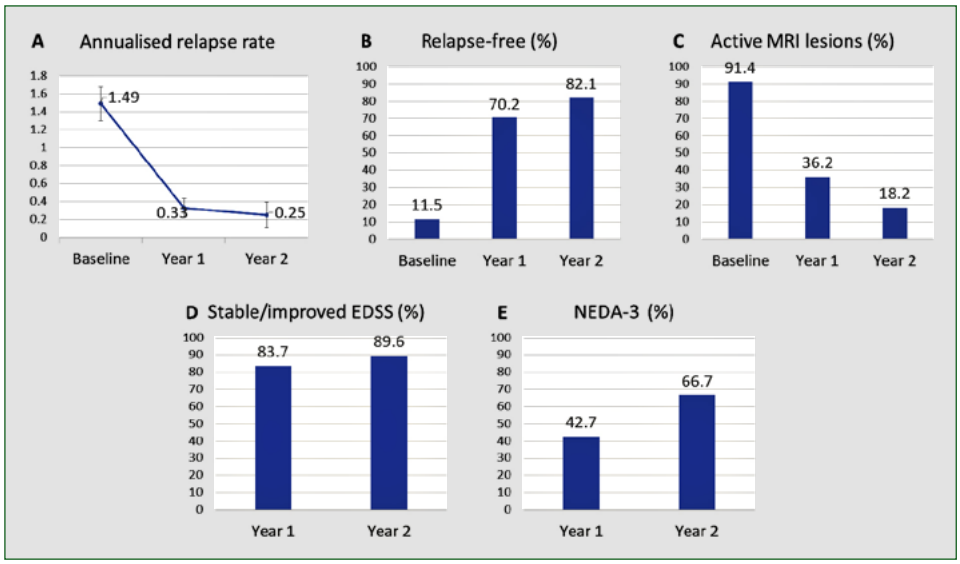

Figure 2. Efficacy outcomes after treatment with cladribine tablets. **A.** Annualised relapse rate — point estimates are means and error bars are standard deviations. **B.** Percentage of relapse-free patients. **C.** Percentage of patients with active MRI lesions. **D.** Percentage of patients with stable/improved EDSS. **E.** Percentage of patients with NEDA-3. Denominators at baseline, year 1, and year 2 were as follows: A and B (139, 94, 28); C (139, 80, 22); D (–, 86, 29); E (–, 89; 24). EDSS — Expanded Disability Status Scale; MRI — magnetic resonance imaging; NEDA-3 — No Evidence of Disease Activity 3

Table 2. Characteristics by NEDA-3 status at 1st and 2nd year of study

Characteristic	
Year 1	N = 89
NEDA-3; n (%)	
Achieved	38 (42.7)
Switchers from 1st line DMT	21 (23.6)
Switchers from 2nd line DMT	14 (15.7)
Not achieved	51 (57.3)
Year 2	N = 24
NEDA-3; n (%)	
Achieved	16 (66.7)
Switchers from 1st line DMT	8 (33.3)
Switchers from 2nd line DMT	7 (29.2)
Not achieved	8 (33.3)

ARR — annualised relapse rate; EDSS — Expanded Disability Status Scale; DMT — disease-modifying therapy; IQR — interquartile range; NEDA-3 — No Evidence of Disease Activity 3; SD — standard deviation

33 (23.7%) had grade 1 lymphopenia, and 32 (23.0%) had normal lymphocyte counts.

Other than lymphopenia, adverse events occurred in 19 patients (13.5% of the cohort). There were three cases of *Varicella zoster* virus infections, urinary tract infections, fatigue, and nausea and two patients reported headaches. There were single cases of Herpes simplex infection, elevated liver enzymes, an unspecified infection, and stomatitis.

Eight patients discontinued treatment with cladribine: five due to inefficacy (all later received ocrelizumab), one due to lymphopenia, and two due to a personal decision. After completing two cladribine courses, one patient developed secondary progressive MS and received mitoxantrone. Seven patients discontinued treatment after two cycles and one after three cycles.

Discussion

This retrospective study looked at clinical and neuroimaging outcomes for a real-world cohort of patients treated with cladribine tablets. The treatment was safe and effective among predominantly treatment-experienced patients, with nearly 95% of patients switching to cladribine tablets from other DMTs. In year 2, over 80% of patients were relapse-free, EDSS was stable or improved in over 80% of patients, and over 60% of patients achieved NEDA-3. There were no substantial safety issues in our study; the rates of adverse events were similar to or below those reported in phase III trials. Our cohort was of a similar age and had a similar baseline disability as in the pivotal CLARITY study, but the proportion of women was greater (78% *vs.* 68%) [7]. In a registry-based study from Finland, the proportion of women among patients who received cladribine tablets was even greater (86%) [13].

The baseline disease activity in our cohort was substantially higher than in the pivotal CLARITY study (ARR of 1.49 in our cohort, ARR of 0.33 in the placebo arm of the CLARITY study); consequently, the on-treatment ARR was also higher in our cohort (~ 0.25 *vs.* 0.15) [7]. This difference is probably because cladribine tablets in our cohort were mostly

given to treatment-experienced patients who had failed other treatments (owing to the reimbursement policy in Poland). Supporting this view, a post hoc analysis of the CLARITY study showed that patients with prior DMT had a significantly lower reduction in the risk of ARR (rate ratio *vs.* placebo, 0.55) than treatment-naïve patients (0.26, p = 0.032) [14]. Only 12% of patients in our cohort were switched to cladribine tablets because of safety concerns, and the rest because of inefficacy, including those who switched from other second-line DMTs. In contrast, only 26% of patients in the cladribine arm of the CLARITY study had previously received DMTs, predominantly low-efficacy drugs such as interferon beta and glatiramer acetate [7]. Post-marketing studies have reported that the ARR after treatment with cladribine tablets are greater among switchers from other DMTs than in treatment-naïve patients, and the ARR was particularly high in those who used many previous DMTs or were switched from second-line treatments [13–15].

Data from other real-world studies shows that cladribine tablets are used in patients with greater disease activity than in the pivotal CLARITY study. In a real-world study from Italy, among 1,236 patients (~80% treatment-experienced), the ARR within 12 months before starting cladribine tablets was ~1.1, decreasing to 0.2 after treatment [14]. Similarly, among nearly 300 patients from Germany (~75% treatment-experienced), the baseline ARR was 1.0, and it decreased to ~0.2 during treatment with cladribine tablets [16]. Similarly, a Finland-based real-world study reported ARR before (1.0) and after treatment (0.1) with cladribine tablets [13]. In a study from Australia where nearly all patients were treatment-experienced, the ARR decreased from 1.4 at baseline to 0.31 at follow-up [17]. The ARRs in our study were greater (1.49 at baseline, 0.25 in 2 years) than those from most previous real-world studies, which can be explained by the stringent reimbursement criteria in Poland.

We observed a similar proportion of patients who achieved NEDA-3 (67%) as in a real-world study from Italy: 64% of patients over a median follow-up of 22- months [15]. We found that cladribine tablets were associated with stabilisation or improvement of disability scores in over 80% of patients in year 1 and nearly 90% in year 2. These figures are similar to those reported in a post-hoc analysis of the CLARITY extension studies for the respective intervals (100%, 94%) [11]. Likewise, in a real-world study from Italy, 97% of patients were progression-free at 12 months after the last cladribine dose [18]. In particular, an early intensive treatment with high-efficacy agents, such as cladribine, as opposed to an escalation strategy, has been associated with favourable disability outcomes [19].

As mentioned above, the higher disease activity in our cohort than in the pivotal trial and other real-world cohorts is likely to be due to the Polish reimbursement policy. In Poland, treatment with cladribine tablets is reimbursed only for patients with disease activity greater than specified in the drug's label, which states that cladribine tablets are indicated in highly active diseases [6]. In treatment-naïve patients, highly active disease is defined as one relapse in the last year and evidence of MRI activity or two relapses in the last year without MRI activity [6, 20]. In contrast, the Polish reimbursement criteria require a treatment-naïve patient to have had two or more relapses and several active lesions in the preceding 12 months (two or more Gd+ lesions and three or more new T2 lesions) [8]. In treatment-experienced patients, a highly active disease might be considered even in patients without relapses, with at least one Gd+ lesion or at least two new T2 lesions [20]. In the Polish reimbursement scheme, treatment-experienced patients need to have two relapses within 12 months of first-line treatment or 1 "severe" relapse within 6 months of starting first-line treatment with two or more Gd+ lesions and three or more new T2 lesions [8]. A post-hoc analysis of the CLARITY study found that patients with two or more relapses in the year before enrollment had a greater relative risk reduction for the occurrence of relapse compared to other patients (relative risk *vs.* placebo, 0.32 *vs.* 0.49, p = 0.068); similarly, they had a greater reduction in the risk of 6-month confirmed disability (hazard ratio *vs.* placebo, 0.18 *vs.* 0.81, p = 0.004) [21].

Treatment with cladribine tablets is an immune reconstitution therapy characterised by the three phases of reduction, repopulation, and reconstitution [22, 23]. The lymphocyte count decreases in the reduction phase, which may be associated with transient immunosuppression, but it regenerates in the repopulation phase, resulting in immune competence that enables normal responses to infections and vaccinations [22–24]. For example, 38 patients treated with cladribine tablets (time from the last dose to vaccination 2–96 weeks) developed humoral responses after anti-COVID-19 vaccinations, and the responses did not depend on the lymphocyte count [25]. The reconstitution phase leads to long-term qualitative changes in the immune system, which results in sustained disease control in the long-term, as was shown in the CLASSIC-MS study with 9–15 years of follow-up [22, 23, 26].

Compared to other oral DMTs (fingolimod, teriflunomide, dimethyl fumarate), cladribine tables have been shown to be associated with a significantly longer time to treatment discontinuation and lower ARRs [27]. A recent network-metanalysis of high efficacy DMTs reported that treatment with cladribine tablets was associated with a greater likelihood of sustained disability improvement compared to all other DMTs assessed (fingolimod, natalizumab, alemtuzumab, and ocrelizumab) [28]. Immune reconstitution therapy with cladribine tablets is associated with a favourable safety profile because immune suppression is transient in the reduction phase, but the risk of adverse events decreases with the repopulation of lymphocytes. In contrast, maintenance DMTs are typically associated with chronic immunosuppression, and the risk accumulates with longer treatment periods. Treatment with cladribine tablets is well tolerated

by patients with MS, which is partly due to a convenient dosing scheme and low monitoring burden. We observed lower rates of adverse events compared to other studies. As a reflection of cladribine's mechanism of action, lymphopenia was the most frequent adverse event, with the lowest levels reached 3–4 months after the start of therapy, followed by a reconstitution of these cells [29]. Of note, reductions in the lymphocyte count following cladribine administration are more gradual compared to the rapid decrease after treatment with monoclonal antibodies [30]. In our cohort, only ~15% of patients had lymphopenia of grade 3 or greater (compared to ~25% in CLARITY). Treatment with cladribine tablets is associated with a long-term reduction of memory B cells that persists after overall lymphocyte counts have recovered from the initial reduction. The risk of infections outside the periods of lymphopenia seems unchanged, suggesting that the sustained clinical effect is not associated with the potential risks associated with immunosuppression [6].

The safety profile of cladribine tablets in our cohort was similar to that reported in the pivotal trial: we observed a similar frequency of *Varicella zoster* virus infections, nausea, and headache. Around 30% of patients had a documented SARS-CoV-2 infection, with no cases of severe disease course, which is in line with previous observations that treatment with cladribine tablets is not associated with a more serious disease course [31]. Similarly, Czarnowska et al. [32] reported that the course of COVID-19 among patients with MS receiving DMTs in Poland was favourable, with similar rates of hospitalisation and death as in the general population. Interestingly, some of the DMTs (interferon-beta, fingolimod) used to treat MS have been investigated as potential treatments for COVID-19 [33]. Cladribine tablets were discontinued in seven patients after two cycles and in one patient after three cycles; thus, these patients did not receive the full dose of 3.5 mg/kg. For patients who experience disease reactivation between doses, the updated ECTRIMS/EAN guidelines recommend giving the full dose of cladribine before switching to other drugs [34]. A higher proportion of patients in our cohort discontinued cladribine tablets (~6%) compared to the pivotal trial (3.5%); in a registry-based study from Finland, 5% of patients discontinued cladribine tablets [13]. The greater frequency of discontinuation in a real-world setting could be related to more active disease than in clinical trials: most patients in our cohort discontinued cladribine tablets due to inefficacy (5/8).

Our study was limited by a small sample size, with a substantial proportion of patients not having a full follow-up. Overall, our data shows that treatment with cladribine tablets reduces the risk of relapse and stabilises disability. These findings add to the growing real-world evidence of the safety and efficacy of cladribine. In conclusion, cladribine tablets proved safe and effective in a real-world setting among primarily treatment-experienced patients with very high disease activity.

Clinical implications/future directions

Cladribine tablets appear to be safe and effective in a real-world setting among primarily treatment-experienced patients with very high disease activity. Therefore, cladribine tablets may be given to patients who have failed previous treatments, including other highly effective DMTs. The safety profile of cladribine tablets in a real-world setting was similar to that observed in the pivotal CLARITY study. Thus, no additional precautions, except for those already included in the drug label, seem necessary.

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Conflicts of interest: *A.S. — in relation to the content of the publication: served as a lecturer and an expert at advisory boards for Allergan, Amgen, Bayer, Novartis, Biogen, Merck, Polpharma, Roche, Teva, and Eli Lilly; A.P.-W. — declares no conflict of interest; E.T.-K. — received compensation for speaking services and support for congress participation from Biogen Poland, Bayer, Novartis Poland, Roche, Merck and Sanofi-Aventis; A.S. — received compensation for speaking services and support for congress participation from Biogen Poland, Bayer, Boehringer-Ingelheim, Novartis Poland, Roche, Merck and Sanofi-Aventis; P.P. — received funding to attend educational events and speaking honoraria from Biogen, Roche, Merck and Novartis; M.A.-S. — received compensation for speaking and consulting services from Biogen, Bayer, Novartis, Roche, Merck, Teva, Sanofi-Genzyme and BMS. None of the consulting agreements are relevant to the submitted work; I.K.-J. — is the principal investigator in clinical trials sponsored by Merck. She also received consultancy fees from Merck; A.K. — received compensation for speaking and consulting services from Biogen, Bayer, Novartis, Roche, Merck, Teva, and Sanofi-Genzyme; M.Ch. — declares no conflict of interest; K.P.-S. — declares no conflict of interest; A.J.-W. — received honoraria for advisory boards and travel grants from Merck, Roche, Teva, Biogen, Novartis, Sanofi and Bayer; H.B.-P. — received advisory board and/or speaker honoraria from Biogen, BMS, Novartis, Merck, Roche and Teva and support for congress participation from Roche and Biogen; K.R. — received honoraria for advisory boards and travel grants from Merck, Roche, Teva, Biogen, Novartis, Sanofi and Bayer.*

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