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Oral pulsed therapy of relapsing multiple sclerosis with cladribine tablets – expert opinion on issues in clinical practice

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ABSTRACT

Background: Oral cladribine is the first oral pulsed therapy licensed for relapsing multiple sclerosis (RMS). Three years after the introduction into the European market, we evaluated practical aspects in the use of cladribine tablets, incorporating the experience gained in routine clinical practice and real-world studies.
Methods: Based on a structured review process, a panel of nine neurologists experienced in MS therapy discussed salient statements regarding the use of cladribine tables. For each statement the level of evidence was determined according to the levels of evidence recommended by the Centre for Evidence-Based Medicine, Oxford. The strength of each expert statement was then evaluated by means of a linear scale from 1 (very strong rejection) to 9 (very strong approval). Votes were collected by a formalized blinded process. Consent was considered to be reached if at least 75% of the experts agreed on a particular statement (i.e. voted for 7-9 points on the linear scale).
Results: . Statements include efficacy in early RMS, risk of side effects and infections, vaccination, pregnancy, and monitoring requirements.
Conclusion: The consented recommendations summarize the practical experience inthe use of cladribine tablets in a real-world setting. These may provide guidance for unanswered questions arising with the introduction of new treatments such as cladribine tablets.

1. INTRODUCTION

As curative interventions remain elusive for relapsing multiple sclerosis (RMS), (Torkildsen et al. 2016) disease-modifying drugs (DMDs) have been the standard of care since the mid-1990s. These immunomodulating or immunosuppressive treatments are administered at regular intervals via different routes, i.e. subcutaneously (interferon beta-1a/-1b, glatiramer acetate), intramuscularly (interferon beta-1a),

Abbreviations: CD, cluster of differentiation; CI, confidence interval; CIS, clinically isolated syndrome; CNS, central nervous system; DMD, disease-modifying drug; EQ-5D, European Quality of Life-5 Dimensions; EDSS, Expanded Disability Status Scale; HIV, human immunodeficiency virus; KM, Kaplan-Meier; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSQOL-54, Multiple Sclerosis Quality of Life-54; NEDA, no evidence of disease activity; QoL, quality of life; PY, patient year; RMS, relapsing multiple sclerosis; SPMS;, secondary progressive multiple sclerosis; TSQM, Treatment Satisfaction Questionnaire for Medication.

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orally (fingolimod, ozanimod, dimethyl fumarate, teriflunomide) or by infusion (natalizumab, ocrelizumab), and therapy is maintained for an unlimited period of time. (Ray-Grant et al. 2018; European Medicines Agency 2020) In contrast, the concept of pulsed therapy implies the administration of a DMD for short periods of time resulting in a long-lasting modification of the immune system without continuous treatment. It implies a removal of immune cell subsets followed by spontaneous modified reconstitution resulting in the downregulation of CNS-specific autoimmune reactivity. (Meuth et al. 2020) The first pulsed therapy became available in 2013 by the regulatory approval of the anti-CD52 antibody alemtuzumab. Two short infusion cycles 12 months apart were shown to induce prolonged relapse-free periods in a major proportion of patients. However, broad adoption of alemtuzumab has been limited by its considerable risks including the development of severe secondary autoimmune diseases. (Ziemssen et al, 2020)

In 2017, oral cladribine was licensed in the European Union as the first oral pulsed therapy. According to a model proposed by Baker et al. 2019, (Baker et al. 2019) treatment with oral cladribine induces sustained depletion of memory B cell subsets which is considered crucial for its therapeutic efficacy. This is accompanied by a limited but more prolonged depletion of CD4+ T cell subsets. Conversely, T regulatory cells, CD8+ T suppressor cells, plasma cells and regulatory B cell subsets are less depleted and repopulate more rapidly. At 96 weeks, the proportion of naïve B-cells was significantly higher in patients treated with oral cladribine versus placebo. (Kalatskaya et al. 2020)

In the pivotal CLARITY trial, oral cladribine has been shown to effectively reduce disease activity as measured by relapses and MRI lesions. It also reduced the risk of disability progression as measured by EDSS progression confirmed after 3 months (hazard ratio: 0.67; $p = 0.02$). (Giovannoni et al. 2010) Furthermore, 44.2% of patients had NEDA-3 status (no disease activity as measured by relapse, disability progression, and MRI parameters) for 96 weeks. (Giovannoni et al. 2011) The risk of conversion to SPMS was reduced by 52% in patients with EDSS ≥ 3.5 ($p = 0.0212$). 60.0% of patients treated with cladribine tablets had no MRI activity (defined as no new T1 Gd+ lesion and no active T2 lesion in cranial MRI) after 2 years compared to 25.0% of the placebo treated patients ($p < 0.0001$). Preliminary analyses from the extension study CLARITY EXT, the efficacy of cladribine tablets was maintained well beyond the actual treatment period for at least another 2 years. (Giovannoni et al. 2019)

Based on the CLARITY and CLARITY EXT trial, a full treatment course of oral cladribine includes two short oral treatment cycles of 8-10 days over two months, one year apart with no further therapy until at least 4 years after initiation of treatment. (European Medicines Agency 2021)

As with all newly licensed treatments there are open questions with regard to the handling and best utilization of this medication. Three years after the licensing and launch of cladribine tablets in the European Union, real-world experience has now been gained during routine use in approximately 17,500 patients comprising close to 15,000 patient years of exposure. (Merck Serono 2020). With Germany being one of the first countries in which cladribine tablets were launched in 2017, many neurologists specialized in the treatment of MS have hands-on experience in the management of this new treatment.

The aim of our panel was to evaluate several practical aspects in the use and management of cladribine tablets, incorporating the experience gained in clinical every-day practice and new results from real-world data. The topics covered by this paper are listed in **table 1**.

2. METHODS

A panel of nine German neurologists specialized in the treatment of MS patients defined the pertaining issues, evaluated the available evidence from the published literature and data presented at recent medical scientific conference, and voted on specific opinion statements developed by the members of the panel. The respective literature and data sources are referenced for each topic.

Table 1
Practical aspects in the use and management of cladribine tablets

1. Timing of oral cladribine in the treatment of RMS
2. Use in patients with a first demyelinating event ("CIS")
3. Use in RMS patients in transition to active SPMS
4. Use in patients requiring a rapid treatment effect
5. Necessity of the second treatment cycle
6. Benefit in patients with residual disease activity on treatment
7. Long-term management of patients after a full course of oral cladribine
8. Risk of infections
9. Use of vaccines
10. Risk of malignancies
11. Timing of pregnancies
12. Monitoring requirements
13. Burden of therapy
14. Effects on quality of life

In terms of voting, the full group of experts convened in a virtual session. The individual statements were first presented by the two chairmen (M. Stangel, S. Schmidt) along with the available evidence, discussed in detail and amended if required. For each statement, the panel first voted based on the level of the available evidence on a scale developed by the Oxford Centre for Evidence-Based Medicine (**table 2**). (Center of Evidence Based Medicine, 2021) The strength of each expert statement was evaluated by a linear scale from 1 (very strong rejection) to 9 (very strong approval). Voting was performed anonymously using the Microsoft Forms software via the meeting chat. Consent was considered to be reached if at least 75% of the experts agreed on a specific statement (i.e. voted in the range of 7-9 points on the linear scale).

The results are reported as mean values. Consensual approval of a statement signifies endorsement as a basis for guidance in the management of MS therapy with cladribine tablets.

3. RESULTS

3.1. Should oral cladribine be used early in the course of MS to increase the likelihood of a maximum therapeutic benefit?

At present, two different treatment paradigms are used in early MS: The "escalation" approach implies the initiation of a treatment with moderate efficacy followed by a switch to a treatment with high efficacy, if required. Conversely, the approach of "early high effective therapy" makes use of a highly effective treatment upfront. (He et al. 2020)

Table 2
Grades of evidence recommended by the Centre for Evidence-Based Medicine, Oxford (Center of Evidence Based Medicine, Oxford, 2021)

1a	Systematic reviews (with homogeneity) of randomized controlled trials
1b	Individual randomized controlled trial (with narrow confidence interval)
1c	All or none case series*
2a	Systematic reviews (with homogeneity) of cohort studies
2b	Individual cohort study or low quality randomized controlled trials (e.g. <80% follow-up)
2c	Outcomes research; ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor-quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Note: A minus sign "–" may be added to denote evidence that fails to provide a conclusive answer because it is either a single result with a wide confidence interval; or a systematic review with troublesome heterogeneity.

* All or none case series: "All patients experienced the outcome (e.g. died) before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it."

3.1.1. Available evidence

Cladribine tablets are licensed for use in adult patients with highly active relapsing multiple sclerosis (MS), defined by clinical or imaging findings. (European Mediciens Agency 2020) This label allows for the application in a wide range of clinical situations.

The inclusion criteria of the CLARITY study required ≥1 relapse in the previous 12 months. A post-hoc analysis investigated a subpopulation comprising patients with high disease activity (defined by ≥2 relapses in the previous year regardless of the MRI lesion load OR ≥1 relapse in the previous year plus ≥1 Gd-enhancing lesion or ≥9 T2 lesions detected by MR imaging). Here, oral cladribine reduced the annualized relapse rate by 67% versus placebo ($p < 0.0001$). The proportion of patients with disease progression confirmed after 6 months was reduced by 82% (hazard ratio: 0.18; 95% confidence interval [0.07; 0.47]). The 10^{th} percentile was reached between week 16 and 23 in the placebo group. It was not reached in the oral cladribine group. (European Medicines Agency 2020)

The two-year double-blind placebo-controlled ORACLE-MS trial (Leist et al. 2014) investigated the use of cladribine tablets in treatment-naïve patients with a clinically isolated syndrome (CIS). In the primary analysis, oral cladribine reduced the cumulative incidence of clinically definitive MS (CDMS, according to criteria defined by Poser et al. (Poser et al. 1983) by 67.3% over 2 years ($p < 0.0001$).

A retrospective international observational study combining data from the MSBase registry and the Swedish MS registry, He et al. (He et al. 2020) showed that a high-efficacy treatment (mostly other than cladribine) initiated within 2 years of disease onset is associated with less long-term (6-10 years) disability accumulation (hazard ratio for EDSS progression confirmed at 6 months 0.34; $p = 0.0001$) compared to patients treated later in the course of the disease (4-6 years after onset). This suggests that the early use of high-efficacy therapies has a beneficial effect on long-term disability.

3.1.2. Expert statement

Clinical studies indicate that oral cladribine is effective in the early phase of MS. However, there is insufficient evidence to decide whether long-term efficacy is improved if oral cladribine is used early, as suggested by data available for other highly effective treatment options.

Level of consensus: 70.0%
Median (mean) strength of recommendation: 7 (7.0)
Level of evidence: 5

3.2. Is oral cladribine an effective treatment after a first demyelinating event (i.e. at clinical onset of MS)?

3.2.1. Available evidence

The benefit of cladribine tablets in patients with a first demyelinating event was demonstrated in a double-blind prospective clinical trial. As explained in section 1, the ORACLE-MS study demonstrated robust efficacy of oral cladribine in people with a first demyelinating event. (Leist et al. 2014) The study data were re-analyzed for a subpopulation fulfilling the McDonald 2010 diagnostic criteria of MS. (Polman et al. 2011) Among these patients, oral cladribine reduced the risk of a second relapse or EDSS worsening (confirmed after 3 months) over two years by 74.2% ($p < 0.0009$). Disease activity measured by the cumulative number of MRI lesions was also significantly reduced (Gd-enhancing lesions -79.4%; $p < 0.0001$), new/active T2 lesions (-68.9%; $p < 0.0001$). (Freedman et al. 2017)

3.2.2. Expert statement

Oral cladribine is highly effective in patients presenting with a first demyelinating event according to the ORACLE trial.

Level of consensus: 100.0%
Median (mean) strength of recommendation: 9 (8.8)
Level of evidence: 1b

3.3. Is oral cladribine an effective treatment option for RMS patients in transition to SPMS (i.e. secondary progression with relapses and/or MRI activity)?

3.3.1. Available evidence

The conversion of relapsing-remitting multiple sclerosis (RRMS) to secondary progressive MS (SPMS) occurs by a gradual transition. Lorscheider et al. (Lorscheider et al. 2016) proposed a diagnostic definition of SPMS based on the EDSS value and preceding relapses: SPMS is present if a patient has at least a 1-point worsening from a previous EDSS ≤5.5 (or a 0.5-point EDSS worsening from a previous EDSS ≥6.0) confirmed over ≥3 months in the absence of relapses, with a minimum EDSS score of ≥4 and a pyramidal FS score of ≥2. Transitional MS according to Kleiter et al. (Kleiter et al. 2020) implies: MS disease duration ≥ 4 years; EDSS 3.0 to 5.0; relapse-independent increase of disability by ≥0.5 points over the previous year or ≥1 point over the previous 2 years; MRI with ≥1 cortical lesion(s) OR evidence of cortical atrophy and/or smoldering lesions; disease activity during previous 2 years with ≥1 clinical relapse or ≥1 new or enlarging T2 lesion on MRI.

Oral cladribine has been shown to reduce both annualized relapse rate and EDSS progression in patients with active SPMS (i.e. SPMS with clinically inflammatory activity) in the ONWARD study comparing the combination of oral cladribine plus subcutaneous interferon beta-1a versus interferon beta-1a alone (note that the combination regimen is not licensed for the treatment of MS). (Montalban et al. 2018)

In SPMS patients with relapses (as defined by McDonald 2005 criteria), (Polman et al. 2005) cladribine used in addition to interferon beta-1a s.c. reduced the annualized relapse rate by 89%, (Montalban et al. 2018) confirming data from an earlier study (Beutler et al. 1996) that used a subcutaneous formulation of cladribine in a different dosage regimen in patients with chronic progressive MS (intravenous cladribine 0.10 mg/kg per day for 7 days as 4 monthly courses for a total dose of 2.8 mg/kg). Each of these studies demonstrated a significant reduction of disease activity in active SPMS.

Furthermore, data reported at conferences from the randomized studies CLARITY and ONWARD indicate a significant reduction of the risk of conversion to SPMS by approximately 50% in patients receiving oral cladribine versus placebo, in both the subgroups of patients with a baseline EDSS score of <3.0 and ≥3.5. (Vermersch et al. 2019) The relapse risk was reduced to a similar extent in both groups (by 60% and 53%, respectively). (Giovannoni et al. 2018)

3.3.2. Expert statement

Oral cladribine is an effective treatment option for patients in the transition phase from RRMS to SPMS (i.e. secondary progression with relapses and/or MRI activity).

Level of consensus: 80.0%
Median (mean) strength of recommendation: 7 (7.3)
Level of evidence: 3a

3.4. Is oral cladribine a suitable treatment option for RMS patients requiring a rapid onset of the disease-modifying effect?

3.4.1. Available evidence

Ideally, effective treatment responses in RMS patients include both early and sustained reductions of disease activity. Upon treatment initiation, oral cladribine induces the depletion of CD19+ B lymphocytes with median nadir values around 1.00 x 10^9 cells/L reached at approximately 8 weeks. (Giovannoni et al. 2010) This finding indicates a rapid onset of the pharmacodynamic effect.

Clinically, this is reflected by a reduction of the annualized relapse rate (ARR) observed within the first 4 weeks after treatment initiation from 0.42 in patients receiving placebo to 0.23 in patients treated with

oral cladribine during the pivotal phase III study CLARITY. (Vermersch et al. 2019) The difference reached significance at week 12 (ARR = 0.20 vs 0.49). Treatment with cladribine tablets shifted the 15th percentile of the time to first relapse to 13.4 months versus 4.6 months in the placebo group ($p < 0.001$). (Vermersch et al. 2019)

Subclinical disease activity as measured by the number of active MRI lesions is significantly reduced within 24 weeks after initiation of oral cladribine vs placebo: 0.07 vs 0.97 Gd+ lesions, and 0.45 vs 1.59 active T2 lesions at 24 weeks. (Comi et al. 2013) The analysis of MRI data from the MAGNIFY study indicates a significant decrease of the Gd+ lesion count from month 2 onwards after initiation of therapy with cladribine tablets in patients with highly active relapsing MS. (De Stefano et al. 2020)

3.4.2. Expert statement

The treatment effect of cladribine tablets starts within the first 24 weeks after initiating treatment. Available evidence is insufficient to further narrow down the exact time of onset.

Level of consensus: 88.9%
Median (mean) strength of recommendation: 9 (7.7)
Level of evidence: 1b

3.5. Is the second cycle of cladribine tablets in year 2 important for long-term efficacy?

3.5.1. Available evidence

Long-term data from CLARITY and the open label extension study CLARITY EXT indicate that the efficacy of cladribine is sustained well beyond the scheduled second treatment cycle (which is completed at month 14), with 85.3% of patients exhibiting a stable or even improved EDSS score at 24-36 months after treatment initiation, and 75.2% at 48-60 months after treatment initiation without any further therapy, as suggested by preliminary reports. (Giovannoni et al. 2019) In line with these findings, patients without further treatment in the CLARITY EXT have similar disease outcomes as compared to those who had received additional treatment cycles in years 3 and 4.

Therefore, it seems plausible that the therapeutic effects of the standard two-cycle regimen are sustained for at least 4 years after treatment initiation. These data demonstrate sustained efficacy of oral cladribine in patients who received the licensed regimen of two cycles, given at a 1-year interval. However, no controlled study has been performed to compare one versus two treatment cycles.

Observational data from the Australian registry MS base (Lizak et al. 2021) including 87 patients with heterogeneous baseline characteristics indicate sustained efficacy of oral cladribine after only one treatment cycle (in these patients, the second cycle in year 2 had been omitted due to a temporary suspension of the drug license). Among the 66 patients in whom EDSS follow-up data were available, approximately 80% remained free of EDSS progression and 65% were free of relapses within the first 2 years after completing a single cycle of oral cladribine.

3.5.2. Expert statements

There is good evidence for the long-term efficacy of oral cladribine after completing the two licensed treatment cycles.

Level of consensus: 100%
Median (mean) strength of recommendation: 8 (8.1)
Level of evidence: 1b

There is insufficient evidence for adequate long-term efficacy after completing only one treatment cycle of oral cladribine.

Level of consensus: 100%
Median (mean) strength of recommendation: 9 (8.4)
Level of evidence: 4

3.6. Will patients with disease activity in year 1 benefit from a second course of cladribine tablets in year 2?

3.6.1. Available evidence

According to data from post-hoc analyses of the CLARITY trial, 92% of the patients without a relapse during the first year of study (i.e. after the first treatment cycle) remained free of relapses in the second year. (Yamout et al. 2020) The proportion of patients in the oral cladribine group who had a first relapse on study declined from 14% in year 1 to 7% in year 2. Among the patients with relapses in year 1 on treatment with oral cladribine, 62% had no further relapse in year 2. In the placebo group, 25% had a first relapse on study in year 1, 18% in year 2. 52% of the patients with a relapse in year 1 had no further relapse in year 2.

The experts discussed that the frequency and severity of relapses in the time before the start of oral cladribine, and the severity of any relapse in year 1 on oral cladribine should be considered in the decision about the continuation of oral cladribine in year 2.

3.6.2. Expert statement

There is low-grade evidence for a benefit of the second oral cladribine treatment cycle in terms of disease activity in patients with a relapse during the first year after treatment initiation.

Level of consensus: 66.6%
Median (mean) strength of recommendation: 6 (5.9)
Level of evidence: 4

3.7. How should patients be managed after completing the 2-year treatment period with oral cladribine?

3.7.1. Available evidence

After completing two cycles of oral cladribine (year 1 and 2), further treatment is neither scheduled nor generally recommended. (Meuth et al. 2020) The effects on relapse rate and disability progression in patients treated with cladribine tablets in CLARITY for 2 years was maintained in years 3 and 4 in CLARITY EXT without further treatment. (Giovannoni et al. 2018a) Furthermore, 75% of patients had stable or improved EDSS in year 5. A range of long-term clinical efficacy and safety data has been collected via follow-up of former study patients since 2010. (Giovannoni et al. 2020, Cook et al. 2019, Patti et al. 2020)

Long-term follow up of participants of CLARITY in the PREMIERE registry revealed that 66% of 941 patients did not receive any further disease-modifying MS therapy over 4.5 years after the last dose of oral cladribine. (European Medicines Agency 2017)

In the CLARINET study, (Cook et al. 2019a) follow-up data from patients who participated in randomized clinical trials on cladribine tablets (CLARITY, CLARITY Extension, ONWARD or ORACLE-MS) across 17 MS centers were obtained from the Italian MS Registry. The time span under observation in the registry was 1-137 months (median 80.3). In this patient population (n = 80), the Kaplan-Meier (KM) estimates for the probability of remaining relapse-free at 12, 36 and 60 months after the last dose of cladribine tablets were 84.8%, 66.2% and 57.2%, respectively. The probability of remaining progression-free at 60 months after the last dose was 63.7%. In the total patient population, the KM estimates for the probability of not initiating another treatment at 12, 36 and 60 months after the last dose of cladribine tablets were 62.2%, 46.7% and 28.1%, respectively. The median time-to-treatment change from the last dose was 32.1 (95% CI 15.5–39.5) months, i.e. approximately 46 months (or close to 4 years) after initiating treatment with cladribine tablets. Follow-up therapies included mostly injectable DMDs, natalizumab, fingolimod and teriflunomide. (Cook et al. 2019a)

A recent interim analysis of the CLASSIC-MS study (n = 147 patients), a long-term follow-up study of the phase III CLARITY(+/-EXT) and ORACLE-MS trials, covers a period of 8.3 to 14.2 years after initiation of treatment with cladribine tablets. (Giovannoni et al. 2020a) After a median follow-up of 10 years, patients had a median EDSS of

3.25, 66.3% of patients had not required further treatment with DMDs, 83.7% did not need a walking aid, and 94.6% did not require a wheelchair.

The analysis of the relapse rates in participants of the CLARITY study over 5 years showed a stable low long-term risk of relapse with yearly rates of 0.10 to 0.17. (Giovannoni et al. 2020b)

If necessary, re-initiation of treatment with cladribine tablets beyond year 4 is compatible with the licensed indication. Meuth et al. (Meuth et al. 2020) suggested a long-term management approach guided by the treatment response which is defined by disease activity and/or disease progression. Accordingly, best possible responders and delayed responders having received the licensed treatment courses in year 1 and 2 are not expected to need any additional MS therapy within the 4 years after treatment initiation, while retreatment may be considered in year 5. Regardless of the time after initiation of oral cladribine, non-responders and partial responders may either receive additional treatment cycle(s) or may be switched to a different disease-modifying drug within the second to fourth year. (Meuth et al. 2020)

If disease activity occurs after year 2 of oral cladribine therapy, disease-modifying drugs licensed for RMS are suitable for use according to individual risk-benefit analysis. However, available evidence is currently limited to case series from cohort studies and data from MS registries. (Lizak et al. 2021)

Alemtuzumab and other immune cell-depleting antibodies should be used with caution after oral pulsed therapy with cladribine tablets and should at least be withheld until lymphocyte counts approach normal levels.

3.7.2. Expert statement

If there is evidence of breakthrough disease after the second year of treatment with oral cladribine, all disease-modifying drugs licensed for RMS patients may be used, in accordance with an individualized risk-benefit analysis including the lymphocyte status.

Level of consensus: 40.0%
Median (mean) strength of recommendation: 6 (5.9)
Level of evidence: 4

3.8. What is the risk of infection in patients treated with oral cladribine, which infections have been observed and how are they managed?

3.8.1. Available evidence

The risk profile for cladribine tablets in MS is based on more than 14 years of clinical studies. (European Medicines Agency 2021, Giovannoni et al. 2010, Clinical Trials, 2021) More than 2000 patients were included in the clinical program of cladribine tablets in MS, with >10,000 patient-years of experience with oral cladribine in total. (Cook et al. 2019) Data from post-approval use confirm the favorable risk profile in 29,869 MS patients. (European Medicines Agency 2021)

In the clinical trial program of cladribine tablets in MS, the incidence rate of infections (cladribine 24.9 vs. placebo 27.1 events per 100 patient-years (PY)) and serious infections (0.8 vs. 0.9/100 PY) was similar in both patients receiving cladribine and those receiving placebo (based on >3400 PY of oral cladribine exposure). (Sorensen 2019) The incidence of influenza infections was not different in cladribine-treated patients versus placebo (2.75 vs. 2.69 cases per 100 PY with lymphopenia grade 0-2; and 3.35 vs. 2.69/100 PY with lymphopenia grade 3-4). Herpes zoster occurred more frequently in patients on oral cladribine (0.83 vs. 0.2 episodes per 100 PY). Most herpes zoster episodes occurred 1-3 years after the start of therapy. (Cook et al. 2019)

The overall incidence of infections and the rate of respiratory infection was moderately increased only in patients with grade 3/4 lymphopenia. Note that in clinical trials (CLARITY, CLARITY EXT), 25% of patients developed grade 3 lymphopenia, while <1% had grade 4 lymphopenia. (Cook et al. 2019) In cladribine-treated patients with grade 3-4 lymphopenia (4.5/100 PY), the incidence rate of herpes zoster was higher than in those with grade 0-2 lymphopenia (0.73/100 PY). Severe, multi-segmental or disseminated herpes zoster infections have not been reported to date. (Patti et al. 2020)

Compared to the combined safety analysis of patients on monotherapy from data from the CLARITY, CLARITY EXT, ORACLE-MS and PREMIERE studies (mean treatment time with cladribine tablets = 194 weeks), the current safety analysis (as of July 2020) based on 18,463 patients treated after approval showed low crude incidence rates of severe infections (crude incidence rate 1.23 per 100 patients (pts), herpes zoster (1.07/100 pts) and opportunistic infections (0.04/100 pts; mostly superficial dermal and mucosal mycoses that resolved with standard treatment). No life-threatening infections and no cases of PML were reported in MS patients treated with cladribine tablets. (Giovannoni et al. 2020)

3.8.2. Expert statement

With the exception of a moderately increased risk of herpes zoster episodes, the overall risk of infections is not increased on treatment with oral cladribine.

Level of consensus: 77.8%
Median (mean) strength of recommendation: 8 (7.4)
Level of evidence: 1a

3.9. What is the approach to vaccination in RMS patients before and on treatment with oral cladribine?

3.9.1. Available evidence

In keeping with the paradigm of "de-risking immunotherapy", (Klotz et al. 2019) verification of the vaccination status – or (re-)immunization if required – against tetanus, poliomyelitis, diphteria, pertussis, pneumococci, varicella zoster virus and other pathogens including the COVID-19 virus SARS-CoV-2 (according to local guidelines) is highly recommended prior to the initiation of treatment with cladribine tablets. This immunization panel should be completed 4 to 6 weeks prior to the initiation of treatment with oral cladribine.

Regarding immunizations required while on treatment, the pivotal role of B cell functions in lasting immunity – e.g. in terms of the immunoglobulin class switch from IgM to IgG and mucosal IgA – and the kinetics of lymphocyte counts after application of a cycle of cladribine tablets should be considered.

Study data on the effects of vaccines in MS patients treated with cladribine tablets are not available as yet. According to the time course of immune cell repopulation observed in clinical trials, a time frame starting at 2 to 4 months after the last dose of treatment cycle in year 1 and ending 4-6 weeks before the treatment cycle in year 2 may be considered for vaccination. Similarly, a possible time frame for immunization may be assumed after 2 to 4 months after the last dose in year 2 and thereafter until any further disease-modifying treatment is initiated.

During and after treatment with oral cladribine, vaccination with live-attenuated vaccines is contraindicated as long as lymphocyte counts remain below the normal range. Immunization with inactivated or subunit vaccines may be performed within the time frames discussed above after treatment initiation. However, there are currently no studies addressing the safety and efficacy of immunization in MS patients receiving treatment with cladribine tablets.

In patients exhibiting no protective antibody responses against the varicella zoster virus (VZV), vaccination with an attenuated VZV vaccine is mandatory prior to initiation of treatment with oral cladribine. To reassess immune responses to the VZV vaccine, measuring VZV-specific antibodies 4-6 weeks after immunization appears appropriate.

For patients with a history of chickenpox or a prior full course of the live attenuated VZV vaccine, a subunit vaccine against VZV reactivation (Shingrix®) is available since 2018. It is licensed for adults of any age with elevated risk of herpes zoster and generally for those at 50 years of age and older. (European Medicines Agency 2020) Since the incidence of

herpes zoster is increased in patients on T- and B-cell depleting monoclonal antibodies, sphingosine-1-phosphate receptor modulators and cladribine, it appears reasonable to use the herpes zoster vaccination in MS patients before starting these therapies.

In the MAGNIFY trial, a 2-year prospective phase IV study in highly-active relapsing MS, 15 patients treated with cladribine tablets received a seasonal influenza vaccine (n = 12) or the VZV vaccine (n = 3) as standard of care less than a month before treatment initiation or during year 1 or 2 at different time points. In the post-vaccination blood samples, the antibody titers were above the limit for seroprotection (hemagglutination inhibition ≥40) for all strains present in the influenza vaccine. Likewise, the antibody titer was above the level of protection (≥100 IU/L) in the post-vaccination samples from the patient receiving the VZV vaccine at all time points examined. (Roy et al. 2021)

3.9.2. Expert statement

From the safety perspective, immunizations with all replication-incompetent vaccines may generally be used at any time in patients treated with cladribine tablets. Recovery of lymphocyte numbers in the treatment-free intermission and after the second treatment course may support vaccine response.

Level of consensus: 66.6%
Median (mean) strength of recommendation: 7 (7.2)
Level of evidence: 5 (9/9)

Immunizations with live-attenuated vaccines are possible 4 to 6 weeks before starting therapy with cladribine tablets. Vaccinations with live-attenuated vaccines should be avoided during the active treatment phase and afterwards until the lymphocyte counts have returned to the normal range.

Grade of agreement: 88.9%
Median (mean) strength of recommendation: 8 (8.0)
Level of evidence: 5 (9/9)

3.10. Is there a relevant risk of malignancies associated with oral cladribine?

3.10.1. Available evidence

Cladribine is a prodrug preferentially activated in lymphocytes due to their nucleoside kinase-to-phosphatase ratio. (Leist et al. 2011, Salvat et al. 2009, Whitmore et al. 2016) 2-chlorodesoxy-adenosine-5'--triphosphate (the active metabolite of cladribine) induces apoptosis in both resting and dividing cells. In resting cells, inhibition of DNA repair enzymes results in DNA strand breaks, resulting in cell death while mitochondrial toxicity leads to apoptosis. (Leist et al. 2011) In dividing cells, cladribine impairs DNA synthesis and direct incorporation into DNA results in chain termination. Thus, surviving cells are highly unlikely to be able to replicate. (Salvat et al. 2009) Induction of malignancies by treatment with oral cladribine is deemed unlikely due to the pharmacodynamics of cladribine, its mode of action, and the short time of exposure to the active substance.

The incidence rate of newly diagnosed malignancies in the cohort of MS patients treated with the licensed dose of oral cladribine in the clinical study program was 0.01 events per patient year, which is well within the age-adjusted incidence reference range observed in cohorts of MS patients (Nørgard et al., 2019) and the general population. (National Cancer Institute 2020) In the post approval setting, the incidence rate was five times lower at 0.002 per patient year. (Cook et al. 2019)

The analysis by Pakpoor et al. (Pakpoor et al. 2015) showed that the unusually low incidence of malignant disease in the placebo arm of CLARITY was the main reason for the observed imbalance in that study. The malignancy rate in patients treated with cladribine tablets (0.34%) was neither increased in comparison to all other treatment groups, nor in placebo-controlled studies (0.6%; p = 0.46) or other studies including patients with an active comparator (0.67%; p = 0.37). An integrated safety analysis for patients exposed to oral or parenteral cladribine during the clinical development program in MS did not provide evidence of an increase in malignancy rates compared to placebo. (Vermersch et al. 2019)

Further epidemiological analyses suggest that the incidence of malignancies in the clinical trial program of cladribine tablets is not increased compared to matched reference populations. (Galazka et al. 2017) A recent safety analysis (July 2020) based on 18463 post-approval treated patients showed a lower crude incidence rate of malignancies than observed in the clinical study program (0.23 vs. 1.08 per 100 patient-years). (Giovannoni et al. 2020) Patients should observe the standard guidelines for cancer screening.

3.10.2. Expert statement

There is currently no evidence of an increased risk of malignant disease in MS patients treated with oral cladribine.

Level of consensus: 100.0%
Median (mean) strength of recommendation: 8 (8.1)
Level of evidence: 1a

3.11. At which time after treatment initiation with oral cladribine can female patients envisage a pregnancy?

3.11.1. Available evidence

While mouse experiments reveal teratogenicity of cladribine upon intraperitoneal administration of dosages ≥5 mg/kg, no signal of teratogenicity emerged from the limited pregnancy data in the oral cladribine clinical trial program with the approved dose. (European Medicines Agency 2020)

According to the current summary of product characteristics of cladribine tablets, (European Medicines Agency 2020) pregnancy must be ruled out in females of childbearing age prior to the initiation of treatment with oral cladribine in years 1 and 2. Dual-method contraception (i.e. hormonal and barrier), is mandatory during treatment cycles with cladribine for 6 months after the last dose.

While contraception is required for the aforementioned periods of time, females may conceive 6 months after completing the second treatment cycle. Females who conceive while on treatment with oral cladribine are advised to discontinue treatment.

It can be surmised that human gametogenesis may be affected by cladribine since it interferes with DNA synthesis. Therefore, male patients must also take precautions during treatment with cladribine for at least 6 months following the last dose of each treatment cycle. Breast-feeding is contraindicated during treatment cycles and for 1 week after the respective last dose, since cladribine has been detected in breast milk. (Datta et al. 2020)

The post-approval pregnancy safety study CLEAR (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance 2021) was initiated to determine if exposure to oral cladribine 6 months prior and/or during pregnancy has an adverse effect on pregnancy and infant outcomes in females with MS, including those pregnancies in which the male parent had been exposed to oral cladribine. Pregnancies in patients without exposure to any DMD will be used as controls.

3.11.2. Expert statement

Women can become pregnant 6 months after the last dose in the second year of therapy with cladribine tablets.

Level of consensus : 88.9%
Median (mean) strength of recommendation: 8 (7.5)
Level of evidence: 4

3.12. What are the monitoring requirements in patients before and on therapy with oral cladribine?

3.12.1. Available evidence

No objective measures are available for a quantitative comparison of the overall monitoring burden in MS patients on different immunomodulatory or immunosuppressive therapies. Based on the CLARITY trial and the label, (European Medicines Agency 2021) the monitoring before and after treatment cycles with oral cladribine includes the following:

- A baseline cranial magnetic resonance scan (not older than 3 months) should be available before initiating oral cladribine.
- Screening for latent infections, in particular tuberculosis and hepatitis B and C, must be performed prior to initiation of therapy in year 1 and year 2.
- Lymphocyte counts must be determined before initiating oral cladribine in year 1, before initiating oral cladribine in year 2, as well as 2 and 6 months after start of treatment in each treatment year.
- If the lymphocyte count is below 500 cells/mm^3, it should be actively monitored until an increase to the normal range is reached.
- In women of childbearing potential, pregnancy must be excluded before the initiation of oral cladribine in year 1 and year 2.
- No mandatory treatment-associated monitoring is scheduled for year 3 and 4.

According to recommendations by the German KKNMS (Clinical Competence Network Multiple Sclerosis) laboratory monitoring prior to the initiation of the two treatment cycles in year 1 and 2 should include differential blood counts, hepatic and renal function tests, serological exclusion of active infections (including hepatis B and C, HIV, and tuberculosis), and confirmation of a sufficient immunity to VZV. Blood counts and liver/renal function tests are suggested every 2-3 months. (Clinical Competence Network Multiple Sclerosis, 2020)

3.12.2. Expert statement

The monitoring requirements for patients treated with oral cladribine are low.

Level of consensus: 66.7%
Median (mean) strength of recommendation: 8 (7.3)
Level of evidence: 5

3.13. Does oral cladribine reduce the burden of therapy in RMS patients versus other highly effective treatment options?

3.13.1. Available evidence

Disease-modifying therapies in MS either require intake of medication at high frequencies and/or invasive routes of application. Oral DMDs are used once to twice daily, injectable DMDs are applied subcutaneously or intramuscularly at frequencies of once daily to biweekly, while antibody therapies are infused at intervals from 4 to 24 weeks.

The treatment regimen of oral cladribine involves two treatment cycles (12 months apart), each comprising two periods of 4 to 5 days, respectively, of oral intake at a 1-month interval. According to the summary of product characteristics, (European Medicines Agency 2021) no further treatment is scheduled for up to 4 years after treatment initiation.

The treatment regimen outlined above may facilitate patient adherence. In line with this assumption, the patient support program (Adveva®) reported 100% consumption of all doses in the first cycle. (Lyons et al. 2019) The ongoing prospective observational study CLICK-MS investigates patient-reported outcomes including the adherence in routine clinical practice. (Miravalle et al. 2019) However, it is difficult to quantify the burden of therapy as it is a rather subjective measure.

3.13.2. Expert statement

Pulsed therapy with cladribine tablets is associated with a low treatment burden on RMS patients.

Level of consensus: 77.8%
Median (mean) strength of recommendation: 8 (6.6)
Level of evidence: 5

3.14. What is the impact of treatment with oral cladribine on the quality of life in RMS patients?

3.14.1. Available evidence

Given its therapeutic efficacy, favorable adverse event profile and application regimen, oral cladribine may be associated with positive effects on quality of life (QoL).

Afolabi et al., 2018 investigated the effect of oral cladribine on two standard quality-of-life measures. In total, 5148 EQ-5D responses and 894 MSQOL-54 physical, mental health and dimension scores were extracted from phase III clinical trial data. Baseline EQ-5D indices correlated with EDSS scores. After 2 years, EQ-5D index scores of RMS patients treated with 3,5 mg/kg oral cladribine were significantly improved compared to placebo ($p = 0{,}001$). Analysis of the individual sub-dimensions of the EQ-5D revealed a significant improvement in the dimension of self-care ($p < 0{,}01$). Conversely, a larger proportion of patients on placebo worsened in the sub-dimensions of mobility and anxiety when compared to those treated with cladribine. A non-significant improvement was also detected in MSQOL-54 scores comparing patients treated with cladribine versus those treated with placebo.

In the ongoing prospective study, CLARIFY-MS, including patients with highly active RMS receiving oral cladribine, the mean TSQM v1.4 global satisfaction scores at 6 months was 70.4, with a side-effect score of 91.9 and a convenience score of 86.6. (Brochet et al. 2020) Another ongoing observational study, CLADQoL, prospectively evaluates the QoL in RMS patients ($n = 298$) receiving oral cladribine. After 12 months, the MSQoL54 physical and mental health component scores remained stable versus baseline. (Penner et al. 2020)

3.14.2. Expert statement

The quality of life of patients treated with cladribine tablets is improved as compared to placebo.

Level of consensus: 88.9%
Median (mean) strength of recommendation: 8 (7.6)
Level of evidence: 1b

4. Discussion

Based on the positive benefit risk ratio of oral cladribine and the data discussed above, the results of this consensus process underscore the benefits of oral pulsed immune therapy with cladribine tablets in clinical practice.

Clinical studies indicate that pulsed therapy with oral cladribine is effective in the early phase of RMS, in patients presenting with a first demyelinating event, and in patients with early active SPMS.

As Meuth and coauthors (Meuth et al. 2020) state in a recent opinion paper, cladribine tablets may have the potential to bring about a paradigmatic shift in MS disease management due to the prolonged disease-free periods and the long-lasting immunomodulation without the need for ongoing treatment. The experience after the first three years of cladribine use in everyday practice supports its further use and the investigation of long-term effects.

Many questions, in particular with regard to long-term efficacy and safety, will only be answered in the future when the first patients are beyond the formal 4-year therapy period after approval. However, published data and the personal experience gathered by this expert

panel are in favour of pursuing the use of cladribine tablets. The statements made here reflect both data from published clinical studies and personal expert opinion and may thus guide others in the use of cladribine tablets.

5. Conclusion

The results of this consensus process underscore the therapeutic potential of Cladribine in clinical practice and provide an expert opinion on the use as one of the treatment options in the course of early to late RMS.

Author contributions

Veit Becker contributed to the acquisition and interpretation of data as well as editing of the manuscript.

Birte Elias-Hamp contributed to the acquisition and interpretation of data as well as editing of the manuscript.

Christoph Grothe contributed to the acquisition and interpretation of data as well as editing of the manuscript.

Joachim Havla contributed to the acquisition and interpretation of data as well as editing of the manuscript

Refik Pul contributed to the acquisition and interpretation of data as well as editing of the manuscript.

Daniela Rau contributed to the acquisition and interpretation of data as well as editing of the manuscript.

Stephan Richter contributed to the acquisition and interpretation of data as well as editing of the manuscript.

Stephan Schmidt co-chaired the project, was involved in the design of the project, interpreted the data, and revised the manuscript.

Martin Stangel co-chaired the project, was involved in the design of the project, interpreted the data, and revised the manuscript.

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