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Review article

Expert opinion on the long-term use of cladribine tablets for multiple sclerosis: Systematic literature review of real-world evidence

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ABSTRACT

Background: Treatment with cladribine tablets (CladT), an immune reconstitution therapy for relapsing multiple sclerosis (RMS), involves two short courses of treatment in Year 1 and Year 2. Most patients achieve sustained efficacy with CladT, but a small proportion may experience new disease activity (DA). Following completion of the indicated dose, physicians may have questions relating to the long-term management of these patients. Since the EU approval of CladT over 5 years ago, real-world evidence (RWE) is increasing and may provide some insights and guidance for clinical practice. We describe a systematic literature review (SLR) of RWE and provide expert opinions relating to six questions regarding the long-term use of CladT.

Methods: Pertinent clinical questions were developed by a steering committee (SC) of 14 international multiple sclerosis (MS) experts regarding breakthrough DA in Year 1, new DA after 2 years or more of treatment, long-term management of stable patients, and whether additional courses of CladT may be required or safe. An SLR was performed in EMBASE and PubMed using the population, intervention, comparators, outcomes, study design (PICOS) framework to identify relevant studies within the last 15 years. Searches of key congress proceedings for the last 2–3 years were also performed. Following review of the results and RWE, the SC drafted and agreed on expert opinion statements for each question.

Results: A total of 35 publications reporting RWE for CladT were included in this review. In the real world, breakthrough DA in Year 1 is of low incidence (1.1–21.9%) but can occur, particularly in patients switching from anti-lymphocyte trafficking agents. In most patients, this DA did not lead to treatment discontinuation. Reported rates of DA after the full therapeutic effect of CladT has been achieved (end of Year 2, 3 or 4) range from 12.0 to

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18.7% in the few studies identified. No RWE was identified to support management decisions for stable patients in Year 5 or later. Views among the group were also diverse on this question and voting on expert opinion statements was required. Only two studies reported the administration of additional courses of CladT, but detailed safety outcomes were not provided.
Conclusions: RWE for the long-term use of CladT in the treatment of RMS is increasing, however, gaps in knowledge remain. Where possible, the RWE identified through the SLR informed expert statements, but, where RWE is still lacking, these were based solely on experiences and opinion, providing some guidance on topics and questions that occur in daily clinical practice. More real-world studies with longer-term follow-up periods are needed and highly anticipated.

Non-standard abbreviations

AAN	American academy of neurology
ACTRIMS	Americas committee for treatment and research in multiple sclerosis
AE	adverse events
ARR	annualised relapse rate
CladT	cladribine tablets
CONy	Controversies in Neurology
DA	disease activity
DMT	disease modifying therapy
EAN	European Academy of Neurology
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EDSS	expanded disability status scale
EU	European Union
Gd^{+}	gadolinium-enhancing
HCP	healthcare professional
IRT	immune reconstitution therapy
MENACTRIMS	Middle East North Africa Committee for Research and Treatment in Multiple Sclerosis
MS	multiple sclerosis
NEDA	no evidence of DA
NfL	neurofilament light chain
PICOS	Population, Intervention, Comparators, Outcomes, Study design
PPMS	primary progressive MS
PRO	patient reported outcomes
RMS	relapsing MS
RWE	real-world evidence
Q	question
SC	steering committee
SLR	systematic literature review
SPMS	secondary progressive MS
UAE	United Arab Emirates
WCN	World Congress of Neurology

1. Introduction

Cladribine tablets (CladT) are approved in Europe for the treatment of adults with highly active relapsing multiple sclerosis (RMS), as defined by clinical and imaging features (Merck, 2022). They are a short-course immune reconstitution therapy (IRT), in which patients require only two treatment courses (cumulative dose of 3.5 mg/kg body weight over 2 years, given as one treatment course of 1.75 mg/kg per year). Each treatment course comprises two treatment weeks, one at the beginning of the first month and one at the beginning of the second month, in each treatment year. Following completion of two treatment courses, no further treatment with CladT is required in Years 3 and 4 (Merck, 2022).

Cladribine selectively targets B and T lymphocytes (Merck, 2022). There is a preferential reduction in certain lymphocyte sub-populations, while leaving the innate immune system relatively spared (Rammohan et al., 2020). The lowest absolute lymphocyte counts occur approximately 2–3 months after the start of each treatment course, followed by a gradual recovery (immune reconstitution) (Comi et al., 2019).

In the CLARITY study, treatment with CladT was associated with significant improvements in clinical and imaging parameters (Giovannoni et al., 2010). In the CLARITY-Extension (CLARITY-EXT) study, 98 patients who received CladT 3.5 mg/kg in CLARITY received placebo for 2 years, and demonstrated durable efficacy at Year 4, with over 73% remaining free of relapses (Giovannoni et al., 2018; De Stefano et al., 2022). During Year 5, Expanded Disability Status Scale (EDSS) score stability was observed in 53.9% of patients, improvement in 21.3% and worsening in 24.7% (Giovannoni et al., 2021). Results of the CLARITY and CLARITY-EXT studies have been comprehensively reported (Comi et al., 2019; Giovannoni et al., 2010, 2018, 2021a, 2021b, 2019; De Stefano et al., 2022; Comi et al., 2018; Cook et al., 2019; Vermersch et al., 2021)

It is clear from clinical studies that most patients achieve sustained efficacy with CladT. However, a small proportion experience relapses, magnetic resonance imaging (MRI) activity and/or disease progression on treatment. Consequently, treating healthcare professionals (HCPs) have unanswered questions relating to the management of patients on CladT, particularly regarding breakthrough disease activity (DA) in Year 1, new DA after the initial 2 years or more of treatment, and whether additional courses of CladT are required or feasible. Clinical evidence and guidance on these issues are lacking.

Following the EU and US approval (in 2017 and 2019, respectively), CladT has gained marketing authorisation in more than 80 countries. As of July 2022, an estimated 56,300 patients have received CladT, with 95,664 patients-years of exposure since approval (Giovannoni et al., 2022). Therefore, publication of real-world-use case studies, cohorts and registry data has become increasingly prevalent, possibly providing answers and guidance to some of these questions. Real-world evidence (RWE) can usually offer more realistic insights into the use, safety and efficacy of a treatment outside of the stringent inclusion criteria (e.g., age, prior treatments, level of DA) of clinical trials.

We performed a systematic literature review (SLR), with a focus on RWE, with the aim of identifying data to help answer six questions relating to the use of CladT:

1 How would you manage a case of reactivation of disease/breakthrough DA within Year 1?
2 How would you manage a patient who has taken the indicated two courses of CladT but has evidence of DA after achieving the full therapeutic effect (end of Year 2, 3 or 4)?
3 How would you manage a patient who has taken the indicated two courses of CladT but has evidence of DA in Year 5 or later?
4 How would you manage a patient who has taken the indicated two courses of CladT and remains stable/no evidence of DA in Year 5 or later?
5 What are the safety considerations for continued treatment with CladT?
6 In the event of continued treatment with CladT, in the context of DA, what are the recommended number of additional courses?

A plain language summary video of this review can be found in the supplementary materials.

2. Methodology

A steering committee (SC) of 14 international multiple sclerosis (MS) experts, co-chaired by Celia Oreja-Guevara and Bassem Yamout, led the programme and agreed on the six clinical questions to be addressed.

An SLR was performed in EMBASE and PubMed on 3 March 2022 using the population, intervention, comparators, outcomes, study design (PICOS) framework to identify relevant studies within the last 15 years. Key word strings were developed for each question. Manual searches of key congress proceedings for the last 2–3 years were also performed (ECTRIMS, EAN, ACTRIMS, AAN, MENACTRIMS, CONy, WCN, European Charcot Foundation).

2.1. Study selection and data extraction

The hits identified through electronic searches were subjected to screening. A systematic approach was applied to identify publications of real-world data relating to each question. A single independent analyst screened the titles/abstracts using the inclusion and exclusion PICOS criteria listed in Table 1. A second independent reviewer screened ~10% of records selected at random to check criteria were being applied consistently. Discrepancies in the screening were resolved by a senior reviewer. Positive exclusion methods were employed to selected records for full text review. Where it was unclear whether the inclusion criteria were met, the article remained in the review until sufficient information was available to determine eligibility. Full texts of all the citations included in the first-pass screening were obtained. All the full text articles were then critically reviewed by an expert to see if they carried information/data relevant to the respective study question. A final list of references was compiled for each study question for inclusion.

2.2. Development of expert opinion statements

Following review of the results and data from the SLR, the SC drafted, refined and agreed on expert opinion statements for each question. For questions 2 and 4, opinions differed within the group; therefore, voting on different versions of draft statements was performed via an online survey. The options with most votes were carried forward. Voting options and results are provided in Tables S1 and S2.

3. Results

The process of study identification and selection is summarised in Fig. 1. Electronic searches yielded a total of 3163 hits after removal of duplicates (n=470), which were screened in the first pass, based on the predefined criteria. A total of 447 references (including congress search results) were included for the full text review, which resulted in identification of 226 relevant publications then reviewed by an expert. Of 49 publications selected for inclusion, eight were common between the questions and six were further excluded due to insufficient data/relevance. Finally, 35 publications reporting the RWE data were selected for inclusion.

Most studies (n=25) were summarised only as abstracts. Studies included those from: Italy (n=9); Germany (n=4); international (n=3); Canada, Norway, Portugal, Spain and Sweden (all n=2); Australia, Argentina, Belgium, Lebanon, Chile, the Czech Republic, Finland, the United Arab Emirates (UAE), and the United Kingdom (UK) (all n=1). The number of patients ranged between 1 and 782, and the median/mean follow up (when reported) ranged from 9 months to 14.4 years. A summary of the relevant real-world studies for each question is provided below and in Tables 2–4. Studies that are relevant for multiple questions have been duplicated within the tables and relevant information for the question provided.

Table 1
Inclusion criteria for the research questions (PICOS).

Domain	Inclusion criteria	Exclusion criteria
Population	RMS patients Previously treated patients/Naive patients	SPMS, PPMS, other diseases
Intervention	Cladribine (oral or tablet)	Parenteral cladribine Any other intervention
Comparators	Any comparator/no comparator	-
Outcomes	Q1: Evidence of disease Year 1 • Reactivation/breakthrough of DA within 1 year • Severe/catastrophic relapse • Lymphopenia + prior treatment - inc. level of lymphocyte depletion post 1st course	Time > Year 1 Studies reporting only safety data
	Q2/3: Evidence of disease end of Year 2, 3, 4 and beyond 4 years • Disease activities in this time frame • Disease relapse • Disease progression • Clinical activity • MRI activity • Annualised qualifying relapse rate • MRI assessed lesions • Number of active MRI lesions • Lymphocyte count • Age of patient at time of relapse	Time < Year 2 Studies reporting only safety data
	Q4: Stable disease or NEDA • Patients remained relapse free or with stable disease • Percentage of relapse-free participants	Patients with relapsed disease Studies reporting only the safety data
	Q5: Safety (retreatment or redosing) • Risk of malignancy • Incidence of malignancies • Incidence of infection (herpes zoster) • Long-term infection rate • Incidence of lymphopenia events	DA, clinical efficacy
	Q6: Event (retreatment or redosing) • Patients receiving additional courses of CladT • Recommended number of courses/cycles • Retreatment with CladT • Redosing CladT	
Study design	• Phase II, III and IV clinical trials • Observational studies • RWE/data • Case reports/case series • Congress abstracts • Systematic review and meta-analysis	Animal, in-vitro studies Pharmacokinetic studies Review articles Letters, notes, editorial, correspondence, opinions Recommendations, consensus, guidelines
Language	English	Non-English

CladT, cladribine tablets; DA, disease activity; MRI, magnetic resonance imaging; NEDA, no evidence of DA; PICOS, Population, Intervention, Comparators, Outcomes, Study design; PPMS, primary progressive MS; RMS, Relapsing MS; RWE, real-world evidence; Q, question; SPMS, secondary progressive MS.

3.1. Q1. How would you manage a case of reactivation of disease/breakthrough DA within Year 1?

3.1.1. Summary of available data: frequency and management of relapses in Year 1

Twenty-one real-world studies reported on the frequency and management of relapses in the first year of treatment with CladT (summarised in Table 2). Sixteen of these reported incidence of relapses within the first year (Annovazzi et al., 2020; Bain et al., 2020; Barbuti et al., 2021; Barros et al., 2020; Celius and Berg-Hansen, 2019; Ciampi et al., 2021; Forsberg et al., 2020; Horáková et al., 2021; Kalincik et al., 2018;

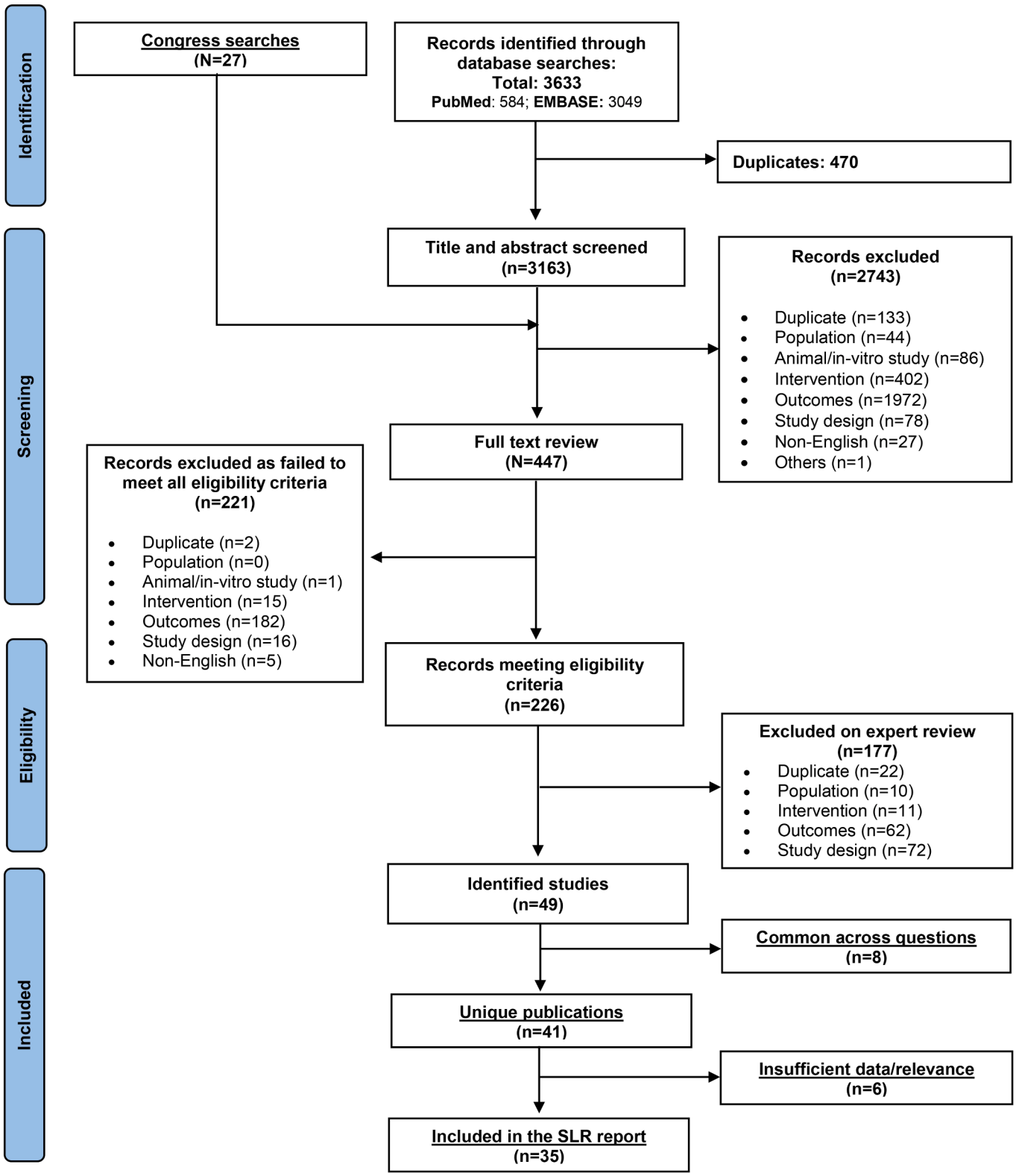

Fig. 1. Modified PRISMA flow.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Pfeuffer et al., 2022, Rojas et al., 2021; Rosengren et al., 2021; Santos et al., 2021, Thakre and Inshasi, 2020; Viitala et al., 2020; Ziemssen et al., 2021) and five reported MRI activity in the first year (Barbuti et al., 2021; Horáková et al., 2021; Rojas et al., 2021; Thakre and Inshasi, 2020; Eichau et al., 2021). The proportion of patients relapsing within the first 6 and 12 months ranged from 1.1 to 10% (Bain et al., 2020; Celius and Berg-Hansen, 2019; Thakre and Inshasi, 2020; Ziemssen et al., 2021) and 4.8 to 21.9% (Annovazzi et al., 2020; Barbuti et al., 2021; Barros et al., 2020; Ciampi et al., 2021, Forsberg et al., 2020; Horáková et al., 2021; Kalincik et al., 2018; Pfeuffer et al., 2022,

Table 2
Summary of results for Q1

Refs.	Study description	N	Disease activity (clinical or MRI)	Discontinuation/switches	Comments
Studies reporting frequency and management of relapses in the first year					
Annovazzi et al. (2020) (Abs)	Italian multicenter retrospective cohort study (mean follow up 12.2 + 5 months)	236	84.7% release free 15.3% relapsed	N/S	-
Bain et al. (2020) (Abs)	Retrospective chart review of Canadian patients	111	11/111 (10%) had ≥1 relapse (at mean 2.3 months post CladT initiation)	0 patients discontinued treatment	-
Barbuti et al. (2021) (Abs)	Italian single center (median follow up 16 months)	60	4/60 (6.7%) had relapses 10/60 (16.7%) developed ≥1 new lesions	1 switch (1.7%) due to lack of efficacy	-
Barros et al. (2020) (Abs)	Observational, multicentric, prospective study from two tertiary hospitals in Lisbon (mean follow up 13 ± 6 months)	85	15 relapses registered in 12 patients (14.1%)	5/85 (5.9%) discontinued treatment in first year due to DA	-
Brownlee et al. (2022) (Abs)	Multicenter, retrospective chart review study (MERLYN)	610	N/S	1 (0.2%) switched within 12 months	-
Butzkueven et al. (2021) (Abs)	Analysis of MSBase registry data	782	N/S	4% discontinuation at 12 months	-
Celius and Berg-Hansen (2019) (Abs)	Post-market cohort from Oslo University Hospital	90	3/90 (3.3%) relapsed within the first 3 months	N/S	2 switchers from fingolimod; 1 treatment naive
Ciampi et al. (2021) (Abs)	Chilean prospective longitudinal multicenter study (median follow up 14 months)	34	4/34 (11.8%) experienced breakthrough disease (multifocal relapse)	2/34 (5.9%) switched to ocrelizumab due to treatment failure	All patients with breakthrough DA were switching from fingolimod
Eichau et al. (2021) (Abs)	Retrospective observational study from a single center in Spain	88	7 (8.0%) with new T2 lesions in the first year	2 (2.3%) switched due to DA	-
Ellenberger et al. (2022) (Abs)	Analysis of CladT-treated patients from the German MS Registry (2017–2021)	390	Within the first 12 months, 58 relapses were recorded in cumulative follow-up time of 320.1 years	N/S	-
Forsberg et al. (2020) (Abs)	Swedish post-market surveillance study (IMSE)	85	2/42 (4.8%) relapsed in 12 months	N/S	42 patients treated for ≥12 months
Horáková et al. (2021)	Analysis of Czech ReMuS registry	436	78.1% free from relapses in first year; 21.9% relapsed; MRI activity was seen in 10.2% in months 0–6 and 10.1% in months 6–12	12/436 (2.8%) switched due to DA or EDSS progression	In Year 1, 17.2% of patients had 1 relapse; 3.7% 2 relapses and 0.9% ≥3 relapses; most mild or moderate
Kalincik et al. (2018)	Propensity score–matched analysis from MSBase	37	Patients free from relapses at end of year 1 ranged from 79–86% (with relapses in 14–21%)	N/S	Patients received only one course of CladT (the drug was withdrawn in Australia in 2011)
Nicholas et al. (2022) (Abs)	Internet-based survey of patients enrolled in the US MS LifeLines patients support programme	616	N/S	1.0% switched in Year 1	-
Pfeuffer et al. (2022)	Prospective cohort from two tertiary centers in Germany	270	40 (14.8%) relapsed within Year 1	3 (1.1%) switched to ocrelizumab due to ongoing DA in Month 12	
Rojas et al. (2021) (Abs)	Sub-study of RelevarEM, a nationwide MS and neuromyelitis optica registry in Argentina (NCT03375177)	102	95.1% free from relapses (relapses in 4.9%) 90.2% free from Gd+ lesions	N/S	-
Rosengren et al. (2021)	Swedish post-market surveillance study (IMSE)	140	5/47 (10.6%) relapsed during first 12 months	3.5% discontinued within Year 1 – no reasons provided (one-year drug survival rate = 96.5%)	Relapse data only available for 47 patients
Santos et al. (2021) (Abs)	Observational, multicentric, prospective study of five tertiary hospitals	182	89% relapse free at 12 months; 11% relapsed	13 (11%) discontinued 9 (7.4%) due to DA	Follow-up data available for 121 patients at 12 months
Thakre and Inshasi (2020) (Abs)	UAE real-world cohort	88	1/88 (1.1%) relapsed after 2 months 1/88 (1.1%) persistent MRI activity at end of year 1	0 discontinued due to DA 1 discontinuation due to pregnancy	-
Viitala et al. (2020) (Abs)	Non-interventional cohort analysis of data from the Finnish MS registry (mean follow up 11 months)	126	8/55 (14.5%) relapsed – mean time to first relapse 6 months (Q1–Q3 1.2–9.8)	3 discontinued (reasons were inefficiency, change of diagnosis and unknown) and 2/55 (3.6%) switched	Subset of patients (n=55) were followed for over a year
Ziemssen et al. (2021) (Abs)	Non-interventional prospective, multicenter study, CLEVER, conducted in Germany	491	10% relapsed within 24 weeks	N/S	-

(*continued on next page*)

Table 2 (*continued*)

Refs.	Study description	N	Disease activity (clinical or MRI)	Discontinuation/switches	Comments
Studies reporting prognostic factors for relapses in the first year					
Annovazzi et al. (2021) (Abs)	Italian multicenter retrospective cohort study (described above)	236	Relapses on CladT more likely in patients switching from other DMTs than those receiving first line CladT (HR 0.2; 95% CI: 0.05–0.7; p=0.01)	N/S	Higher baseline ARR predicted clinical activity on treatment (HR 1.9, 95% CI: 1.2–2.9; p=0.04)
Möhn et al. (2019)	Retrospective chart review in a single center in Germany (median follow up 9.7 months)	17	0/17 (0%) patients switching from natalizumab to CladT experienced a clinical relapse 2/17 (11.8%) showed a new T2 lesion on MRI within 3 months	0 discontinued	-
Nygaard et al. (2022)	Retrospective cohort study from two university hospitals in Oslo of patients switching from fingolimod	33	7 (21.1%) had rebound disease following switch from fingolimod to CladT	N/S	Younger age and previous high relapse rate were associated with increased risk of rebound in the CladT group
Petracca et al. (2022)	Retrospective observational analysis of eight tertiary MS centers in Italy (2-year follow-up study)	243	Patients with a higher number of prior therapies were less likely to retain NEDA-3 status on CladT Mean number (range) of previous DMTs was 1.5 (0–7) Majority of patients were treatment naive (29.3%) or switched from DMF (29.7%)	N/S	Association between baseline characteristics and NEDA-3 was tested via logistic regression models. Each model included several covariates: sex, age at CladT start, disease duration, number of prior treatments, relapses in the year prior to CladT, presence of basal active lesions, basal EDSS, basal lymphocytes, switch or naive status.
Pfeuffer et al. (2022)	Prospective cohort from two tertiary centers in Germany (described above)	270	12/23 (52.3%) patients switching from natalizumab had rebound DA within first 6 months	-	Multivariate analysis was conducted using the Cox proportional hazards model. Sex, age at baseline, last previous DMT, baseline EDSS, baseline relapse rate and disease duration were used as covariates in an enter method.
Zanetta et al. (2021)	Italian real-life cohort	60	Treatment naive patients were more likely to achieve NEDA-3 with CladT that those switching from other DMTs	N/S	-
Zhong et al. (2021)	MSBase registry analysis	333	17 patients (5.1%) relapsed during the washout period and 24 (7.2%) relapsed within one year of starting CladT	Of those who relapsed during their washout period, seven (41.2%) also relapsed on CladT, compared to 5.4% of those who did not experience a washout relapse	Relapse on CladT was predicted by washout relapse (HR=7.18, 95% CI = 1.48-34.88, p=0.015) and younger age (HR=0.96, 95% CI 0.93-0.99, p=0.038). Washout durations longer than two months increased relapse risk during the washout but did not alter relapse risk on CladT. Cox proportional hazard regression models were used to analyze time to first relapse in the first year of CladT.
Other studies of interest/relevance					
Garbo et al. (2021)	Case report of a patient experiencing considerable DA during first year of treatment with CladT	1	Patient switched from fingolimod after a 9-week washout period Relapse and MRI activity (new Gd+ enhancing lesions)	Patient switched to alemtuzumab	

Abs, abstract; ARR, annualised relapse rate; CladT, cladribine tablets; CLEVER, CLadribine Tablets – EValuation of thERapy satisfaction; CI, confidence interval; DA, disease activity; DMF, dimethyl fumarate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; HR, hazard ratio; IMSE, immunomodulation and multiple sclerosis epidemiology; MERLYN, MavEnclad Real-worLd comparative efficacY non-iNterventional; MRI, magnetic resonance imaging; MS, multiple sclerosis; NEDA, no evidence of disease activity; N/S, not specified; UAE, United Arab Emirates.

Table 3
Summary of results for Q2.

Refs.	Study description	N	Disease activity (clinical or MRI)	Switches/additional course	Comments
Studies reporting frequency and management of relapses in Years 3 and 4					
Annovazzi et al. (2020)	Italian multicenter retrospective cohort study (mean follow up 21.1 +7.6 months)	236	81.3% relapse free at follow up (18.7% relapsed) 56.6% reached NEDA at follow up	N/S	-
Ellenberger et al. (2022) (Abs)	Analysis of CladT-treated patients from the German MS Registry (2017–2021)	390	Within 12–36 months after CladT initiation, 50 relapses were recorded in cumulative follow-up time of 289.5 years	Atypical cessation of CladT was reported in 23 patients during the 4-year observation period; insufficient efficacy was the reason in 17 (73.9%) patients	In 30 patients who started another DMT after cessation of CladT, 18 (60%) switched to ocrelizumab
Oreja-Guevara et al. (2022) (Abs/poster)	Observational prospective study in Spain	100	88% relapse free in Years 3/4 (12% relapsed)	N/S	Of 7 patients who relapsed, 6 received an additional (third) course of CladT
Patti et al. (2020)	CLARINET-MS – a non-interventional, retrospective, exploratory analysis of patients from the Italian MS Registry	80	84.8% relapse free 12 months after last dose (Year 3) (15.2% relapsed)	Probability of not initiating another DMT 12 months after the last dose was 79.4%	Includes 34 patients from CLARITY study
Pfeuffer et al. (2022)	Prospective cohort from two tertiary centers in Germany	270		5/142 patients received additional courses of CladT (months 24, 25, 28, 34 and 36, respectively) due to ongoing DA	142 patients in the cohort passed month 24
Other studies of interest/relevance					
Lizak et al. (2021)	Australian Product Familiarisation Program with a median follow up of 3.5 years	90	Over two-thirds of patients with RRMS (67%; n=47/70) received an alternative DMT after CladT during the follow-up period, 26% of whom (n=12/47) experienced relapses prior to switching, but 74% (35/47) switched before a relapse	The median (95% CI) time to next DMT in the RRMS cohort was 1.16 years (1.06–1.79)	Due to the withdrawal of the commercially available product before the second year of treatment was due, the 87 patients only received the first year of CladT treatment

Abs, abstract; CI, confidence interval; CladT, cladribine tablets; DA, disease activity; DMT, disease-modifying therapy; MS, multiple sclerosis; NEDA, no evidence of disease activity; N/S, not specified; RRMS, relapsing-remitting multiple sclerosis.

Table 4
Summary of results for Q3.

Reference	Study description	N	Disease activity (clinical or MRI)	Switches/additional course	Comments
Studies reporting frequency and management of relapses beyond Year 4					
Dive et al. (2020) (Abs)	Long-term outcomes in patients from single center in Belgium included in the CLARITY and CLARITY-EXT studies	10	No additional therapy required in 70% patients – remained NEDA-3 30% relapsed within 5 years	30% switched due to DA (within 5 years)	14.4 years mean time of follow up
Giovannoni et al. (2021)	CLASSIC-MS – an exploratory, low-interventional, ambispective phase IV study of patients previously enrolled into phase III parent trials	394	No evidence of disease reactivation was observed in 50.3% (198/394) of patients exposed to CladT in 4 years since last dose (Year 5)	55.8% (220/394) of the exposed cohort received no subsequent DMT during follow up	Median follow up of 10.9 years since last dose
Patti et al. (2020)	CLARINET-MS (described above)	80	66.2% relapse free 36 months after last dose 58.9% relapse free 60 months after last dose	Probability of not initiating another disease-modifying treatment 36 and 60 months after the last dose was 55.6% and 32.4%, respectively	Median time to treatment change from last dose in CLARITY patients – 37.1 months
Yamout et al. (2020) (Abs)	Long-term outcomes in patients from single center in Lebanon included in the CLARITY and CLARITY-EXT studies	24	3/22 patients had an EDSS increase over the whole follow-up period, 13 had a decrease and 6 were stable	13/22 patients started a new DMT during follow up; reasons for these treatment switches are not provided	Follow-up time was 9.8 years
Other studies of interest/relevance					
Moccia, et al. (2020)	Retrospective analysis on prospectively collected data from a single center. Follow up of patients from the phase II/III trials for CladT	13	Time to post-trial relapse 5.4 ± 3.4 years for CladT	Approximately 70% of patients were treated with an additional DMT after trial termination, of whom ~20% received a second-line post-trial DMT	From baseline to Year 4, patients treated with CladT showed reduced relapse risk, vs placebo (HR=0.062, 95% CI 0.004–0.937; p=0.045), while no differences were found from Year 4 to Year 8 (HR=4.006, 95% CI 0.415–38.636; p=0.230)

Abs, abstract; CI, confidence interval; CladT, cladribine tablets; DA, disease activity; DMT, disease-modifying therapy; EDSS, expanded disability Status Scale; HR, hazard ratio; NEDA, no evidence of disease activity.

Rojas et al., 2021; Rosengren et al., 2021; Santos et al., 2021; Thakre and Inshasi, 2020; Viitala et al., 2020), respectively.

Details of MRI outcomes (T2 and gadolinium enhancing [Gd+] T1) varied among studies. Barbuti et al. (2021) reported ≥ 1 new lesion in 16.7% of patients (*n*=60). Eichau et al. (2021) reported 8.0% of patients with new T2 lesions in the first year and Rojas et al. (2021) observed

new Gd+ lesions in 9.8% of patients. Non-specified MRI activity was reported in 10.1% of patients by Horáková et al. (2021) and 1.1% of patients in a real-world UAE cohort (Thakre and Inshasi, 2020). Details and timing of rebaselining scans were not provided in these studies, which may account for differences in rates of MRI activity within the first year.

Fourteen studies reported on discontinuation/switch rates within the first year; rates ranging from 0–11%. Discontinuations/switches due to ongoing DA were reported in 0–7.4% (Barbuti et al., 2021; Barros et al., 2020; Ciampi et al., 2021; Horáková et al., 2021; Pfeuffer et al., 2022; Santos et al., 2021; Thakre and Inshasi, 2020; Eichau et al., 2021). Two studies reported subsequent disease-modifying therapies (DMTs); Ciampi et al. (2021) reported that 2/34 (5.9%) of patients switched to ocrelizumab due to CladT treatment failure and similarly, Pfeuffer et al. (2022) detailed a switch to ocrelizumab in 3/270 (1.1%) of patients, due to ongoing DA. In general, treatment discontinuations and switches were lower than relapse rates, suggesting that relapses on treatment during Year 1 did not necessarily lead to discontinuation, with most patients remaining on treatment since the full therapeutic potential of CladT is not achieved until after the second course.

3.1.2. Summary of available data: prognostic factors for relapses in Year 1

Seven studies reported on possible prognostic factors for relapse in the first year of treatment with CladT (summarised in Table 2); the majority were naive indirect comparisons. Annovazzi et al. (2021) reported on 236 patients from 56 MS centers and found that relapses were more likely in patients switching from other DMTs than in those receiving CladT as first DMT (p=0.01). Furthermore, a higher baseline annualised relapse rate (ARR) predicted clinical activity on treatment (p=0.04).

There were conflicting reports of breakthrough DA when switching from natalizumab. Pfeuffer et al. (2022) found that patients switching to CladT from natalizumab were prone to rebound DA, observed in 18/23 patients (median washout time before starting CladT was 66 days). Of those, 12 experienced this within the first 6 months. In contrast, Möhn et al. (2019) observed no clinical relapses in 17 patients switching from natalizumab to CladT (mean washout of 16 weeks).

Treatment-naive patients were more likely to achieve no evidence of DA (NEDA)-3 with CladT than those switching from other DMTs (Zanetta et al., 2021) and retention of NEDA-3 status correlated with a lower number of prior therapies (Petracca et al., 2022) in real-world analyses of Italian patients. Zhong et al. (2021) described 333 patients from the MSBase registry who switched to CladT from a prior DMT (DMF, teriflunomide, fingolimod or natalizumab), with a mean washout of 43.1 days. Relapse on CladT was predicted by washout time (p=0.015) and younger age (p=0.038). Washout durations longer than two months increased relapse risk during the washout, but did not alter relapse risk on CladT (Zhong et al., 2021). Nygaard et al. (2022) found that younger patients with previous high relapse rate were at increased risk of rebounding when switching from fingolimod to CladT.

3.1.3. Expert opinion on management of reactivation of disease/ breakthrough DA within year 1

- In the real world, reactivation of disease, or breakthrough DA, is of low incidence (1.1–21.9%) but can occur within the first few months of treatment with CladT, particularly in patients switching from anti-lymphocyte trafficking agents (e.g., fingolimod, natalizumab)
- Real-world data suggest that patients with a higher baseline ARR, prior DMT treatment, younger age and who relapsed during the washout period had an increased risk of relapsing on CladT
  - For patients who are switching from anti-lymphocyte trafficking agents we recommend frequent monitoring of lymphocyte counts and a washout of no more than 4 weeks
- RWE suggests that in most patients, DA within the first year does not lead to treatment discontinuation (rates of discontinuation due to DA range from 0 to 7.4%), indicating that most patients receive the second course of CladT as planned
- It is recommended that patients receive the full indicated cumulative dose (2 courses) of CladT
  - The exception to this would be in rare situations where DA is unabated or paradoxically increased, in which case we recommend switching to another high-efficacy DMT
  - A patient's prior DMT and level of DA pre-CladT should be taken into consideration when making any treatment decisions

3.2. Q2. How would you manage a patient who has taken the indicated two courses of CladT but has evidence of DA after achieving the full therapeutic effect* (end of Year 2, 3 or 4)?

*The full therapeutic effect: proposed to be 3–6 months after the second course of treatment with CladT (to coincide with the lymphocyte nadir post-second course)

3.2.1. Summary of available data

Five studies reported DA in patients during the time after which the full efficacy of CladT had been achieved (end of Year 2, 3 and 4) (Pfeuffer et al., 2022; Annovazzi et al., 2021; Ellenberger et al., 2022; Oreja-Guevara et al., 2022; Patti et al., 2020). These studies are summarised in Table 3.

Relapses during this time occurred in 12.0–18.7% of patients. Information regarding the management of relapses during this time and the outcomes for patients who relapsed was limited. Oreja-Guevara et al. (2022) reported that 6/7 patients who relapsed in Year 3/4 received an additional (third) course of CladT. Pfeuffer et al. (2022) also reported that 5/142 patients received additional courses of CladT (in months 24, 25, 28, 34 and 36, respectively) due to ongoing DA. Within 4 years of CladT initiation, 23/390 (5.9%) patients from the German MS Registry discontinued CladT treatment; ocrelizumab was the most common subsequent DMT (18/30) in those initiating another treatment (Ellenberger et al. 2022). In the Italian MS registry, the probability of switching to another DMT at the beginning of Year 3 was around 20% (Patti et al., 2020). Reasons and outcomes for any switches during this time were not provided.

3.2.2. Expert opinion on management of DA at the end of Year 2, or in Year 3 or 4

- RWE is scarce and follow-up time inconsistent, but reported rates of DA after the full therapeutic effect of CladT has been achieved (end of Year 2, 3 or 4) range from 12–18.7%
- In the event of new DA during this time consider:
  - Additional courses of CladT*
    - To avoid risks associated with lymphopenia, patient lymphocyte counts should be at least 800 cells/mm^3 before initiating another treatment course

OR

  - Switching to another DMT. There are no contraindications for subsequent DMTs following CladT
    - Follow-up therapy should be based on patient-related and immunological considerations, but usually includes either a B-cell depleter or transmigration blocker. Potential additive effects on the immune system should be considered when choosing subsequent DMTs
- Factors such as level or severity of DA, the timing of DA in relation to last course of CladT, and prior response of patient to CladT should be taken into consideration when making treatment decisions

*There are no label contraindications for additional courses of CladT

in Years 3 and 4; however, this may depend on country-specific considerations on reimbursement or on-label status

3.3. Q3. How would you manage a patient who has taken the indicated two courses of CladT but has evidence of DA in Year 5 or later?

3.3.1. Summary of available data

Four studies reported on longer-term efficacy beyond Year 4 of treatment with CladT (Patti et al., 2020; Dive et al., 2020; Giovannoni et al., 2021; Yamout et al., 2020) summarised in Table 4. They all reported long-term, real-world follow up of patients who took part in the clinical trials for CladT; DA was reported in 30–50% of patients.

Patti et al. (2020) reported outcomes from 80 patients in the Italian MS registry (CLARINET-MS) who had completed ≥1 full course of CladT. Median follow up was 80.3 (1–137) months. The probability of being relapse free was 66.2 and 57.2% at 36 and 60 months after the last dose of CladT, respectively (end of Year 4/Year 6). The probability of being free from disability progression was 73.3 and 63.7% at 36 and 60 months, after the last dose of CladT, respectively, and the probability of not initiating another treatment was 55.6 and 32.4%. Median time from last CladT dose to new DMT was 32.1 (95% confidence interval [CI 15.5–39.5]) months, although no reasons for DMT switches were provided.

Dive et al. (2020) described long-term outcomes from 10 patients included in the CLARITY/CLARITY-EXT studies. Over 14 years, 7/10 patients didn't require additional therapy after CladT. Three patients relapsed within 5 years and moved to other treatments.

Yamout et al. (2020) assessed long-term outcomes for 24 Lebanese patients who received CladT in CLARITY. The follow-up time was 9.8 years (standard deviation [SD]=2). Of 22 patients, 13 started a new DMT during follow up; reasons for these switches were not provided. The ARR was 0.20 (95% CI 0.12–0.33) during the study and 0.20 (95% CI 0.14–0.29) during the post-study follow up

Giovannoni et al. (2021) described the CLASSIC-MS study, assessing 435 patients with a median follow up of 10.9 years (range 9.3–14.9), including 394 who were exposed to CladT in CLARITY and 41 patients who received placebo. For patients who received CladT 3.5 mg/kg over 2 years (n=160) findings suggested numerical improvements in mobility and disability outcomes. Additionally, 58.1% of these patients used no subsequent DMTs, compared to 26.8% of patients in the placebo group.

Moccia et al. (2020) detailed an 8-year follow up of 27 Italian patients from the phase II or III trials (n=13 for CladT; n=14 for placebo). Time to post-trial relapse was 4.5 ± 2.9 years for placebo and 5.4 ± 3.4 years for CladT. Approximately 70% of patients were treated with an additional DMT after trial termination, of whom ~20% received a second-line post-trial DMT. Between baseline and Year 4, patients treated with CladT presented with reduced relapse risk vs placebo (p=0.045). However, no differences were found between Year 4 and Year 8 (p=0.230). This is possibly due to the use of other DMTs in the absence of long-term efficacy data for CladT at the time of study conduction, and possibly due to reduced efficacy of CladT after 4 years. While this study is of interest, few conclusions can be drawn since the population included patients from the ORACLE-MS and ONWARD studies, who had either clinically isolated syndrome, or received CladT in combination with interferon.

3.3.2. Expert opinion on management of DA in Year 5 or later

- RWE is scarce and variable, but reported rates of DA range from 30–50% within 5 years of last dose or end of study
- Long-term responders to CladT (more than 4 years) can be administered additional courses of CladT in Year 5 or later in case of new DA
- There are no label contraindications for additional courses of CladT in Year 5 or later

3.4. Q4. How would you manage a patient who has taken the indicated two courses of CladT and remains stable/no evidence of DA* in Year 5 or later?

*NEDA refers to no clinical relapses, no disability progression (EDSS) and no MRI activity

3.4.1. Summary of available data

There were no real-world studies identified that described management of stable patients beyond Year 4. However, a study of interest is by Lizak et al. (2021). This report included 70 patients with relapsing-remitting MS (RRMS) from the Australian Product Familiarisation Program (median follow up 3.5 years), who received only the first year of CladT due to withdrawal of the commercially available product before the second year of treatment was due. Over two-thirds of patients (67%; n=47/70) received an alternative DMT after CladT during the follow-up period, 26% of whom (n=12/47) experienced relapse prior to switching. It is difficult to draw conclusions from this study since patients did not receive the full cumulative dose. However, of interest is that 74% of patients (35/47) switched from CladT to another DMT before a relapse.

3.4.2. Expert opinion on management of stable disease in Year 5 or later

- Recommend no further treatment, with regular, close monitoring (MRI every 6–12 months, assessment of patient-reported outcomes [PROs], such as fatigue, bladder function and cognition, and biomarkers, such as neurofilament light chain [NfL])*

*This scenario was the most debated, with a few experts considering CladT treatment continuation treatment under certain circumstances (see discussion and Table S2 for further information)

3.5. Q5. What are the safety considerations for continued treatment with CladT?

3.5.1. Summary of available data

Two studies reported additional courses with CladT. Oreja-Guevara et al. (2022) reported that an additional course of CladT in six patients was well tolerated, with only very mild adverse events (AEs), no cases of serious or opportunistic infections, and no Grade 4 lymphopenia. Pfeuffer et al. (2022) also detailed 5/142 patients who received additional courses of CladT due to ongoing DA, but no safety information was provided.

An additional study of interest is from Butzkueven et al. (2021), reporting outcomes from 16 MS patients in Australia treated with CladT 1.75 mg/kg in 2010–2011, and again in 2018. These patients have now received three courses, but with a long treatment gap (approx. 9 years) between courses 1 and 2. Of 11 patients with recorded lymphocyte counts post CladT, none recorded Grade 4 lymphopenia, and five patients recorded Grade 3 lymphopenia. One patient experienced an episode of herpes zoster (shingles).

In the absence of real-world data, it may be useful to consider integrated long-term safety data from the clinical development programme for CladT and the PREMIERE registry. The most recent analysis included 923 patients who received CladT monotherapy (3.5 mg/kg) (Leist et al., 2020). This confirmed a low level of serious treatment-emergent AEs. No new major safety findings were identified, and no new/significant AEs emerged during long-term follow up (Leist et al., 2020). No increased malignancy risk over time and no clustering of malignancies of a particular type were identified in the monotherapy cohort or in the all exposed cohort (n=1976) (which included patients receiving higher doses than those recommended in the EU SmPC) over >8 years (Merck, 2022; Cook et al., 2019). Rates of malignancies were similar to those of a GLOBOCAN matched reference population, and to those observed with other DMTs (Cook et al., 2019).

In CLARITY-EXT, 186 patients received two additional courses of CladT (7 mg/kg cumulative dose), 12 months apart, with a mean gap between courses 2 and 3 of 42.08 weeks (SD 25.37) (Giovannoni et al., 2018). Over 40% of these patients had Grade 3 or 4 lymphopenia, which was persistent. It is important to mention that in CLARITY-EXT there was no stipulation for a minimum lymphocyte count of 800 cells/mm^3 before reinitiation of CladT, which is now specified in the label (Merck, 2022). In patients with ⩾800 cells/mm^3 prior to administration of additional courses, the incidence of lymphopenia dropped to 11% and 12% in Years 3 and 4, respectively (Cook et al., 2017).

3.5.2. Expert opinion on the safety of treatment continuation with CladT

- Real-world data on additional courses are rare, but in general additional courses of CladT have been well tolerated
- There are no longer-term malignancy or infection concerns to date following two courses of CladT, and no increased rates of malignancies or infections in patients receiving higher and additional courses of CladT during the clinical studies, however, risks after additional courses in the real-world remain largely unknown
  - Screening for infections and malignancies should be followed as per the indicated label or according to local screening recommendations. Patients must meet the criteria for initiating/continuing treatment, including a lymphocyte count of at least 800 cells/mm^3 before initiating another treatment course to avoid risks associated with lymphopenia

3.6. Q6. In the event of continued treatment with CladT, in the context of DA, what are the recommended number of additional courses?

3.6.1. Summary of available data

There were no real-world studies comparing one versus two additional courses of CladT. As discussed in the results for Q2, additional courses in a small number of patients have been reported in two studies (Pfeuffer et al., 2022; Oreja-Guevara et al., 2022). One and two additional courses have been used effectively with an acceptable safety profile in the real-world and clinical trial settings.

3.6.2. Expert opinion on additional courses of CladT

- The recommended cumulative dose* of CladT is 3.5 mg/kg body weight over two years, administered as one treatment course of 1.75 mg/kg per year
- One and two additional courses of CladT have been used safely,† however, long-term follow up for safety and efficacy is still lacking in the real-world
- We recommend administering a minimum of one additional course of CladT with the possibility of a second course depending on clinical response
  - Two additional courses are generally not recommended unless DA is not controlled with one additional course

*Each treatment course consists of two treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. A treatment cycle consists of two treatment courses

†The safety of two additional courses has been tested in a phase III clinical study (CLARITY-EXT), with an average interval of approximately 1 year between the second and third course.

4. Discussion

This is, to our knowledge, the first SLR of RWE for CladT. The studies identified provided some guidance for three of the six questions (Q1–3). For the remaining questions (Q4–6), evidence is still lacking, and expert statements are based more on opinion than data. The studies identified support the low relapse and discontinuation rates observed in the clinical studies of CladT.

The largest number of real-world studies identified were for Q1, regarding the management of reactivation of disease/breakthrough DA in the first year. Breakthrough DA is a known phenomenon, particularly when switching from fingolimod or natalizumab (Barry et al., 2019; Prosperini et al., 2019) and appears to occur in some patients irrespective of subsequent DMT. Relapses in the first 12 months of real-world treatment with CladT occur in a minority of patients, and do not normally lead to treatment discontinuation (Barbuti et al., 2021; Barros et al., 2020; Ciampi et al., 2021; Horáková et al., 2021; Pfeuffer et al., 2022; Santos et al., 2021; Thakre and Inshasi, 2020; Eichau et al., 2021) suggesting low-level DA in most cases. Rarely, a severe rebound may be observed where DA is unabated or paradoxically increased, versus pre-treatment levels. Several treatment strategies have been employed to manage such severe relapses/rebound including corticosteroids, plasma exchange and anti-CD20 B-cell depletion (Barry et al., 2019) as well as applying shorter washout periods upon switching from anti-lymphocyte trafficking agents (Pardo and Jones, 2017; Goncuoglu et al., 2021; Korsen et al., 2022).

Expert agreement on statements was achieved on 4/6 questions without the need for voting. While the group agreed on most of the expert opinion for Q2, voting was needed for a statement on subsequent DMTs (Table S1). Voting was also required for Q4, regarding the management of patients who have taken two courses of CladT and who remain stable in Year 5 or later. Most experts (9/14) would prefer close monitoring of stable patients, with regular assessment of multiple indicators of DA (MRI activity, EDSS, PROs, NfL levels) and consideration of additional CladT courses in the event of DA. This approach, in their opinion, aligns with the concept of IRT, which is to induce long-term disease stability/remission (Sellner and Rommer, 2020; Sorensen and Sellebjerg, 2019). Indeed, long-term follow up of patients enrolled in the CLARITY and ORACLE trials showed that a proportion of patients can remain stable without DA and no further treatment for 5–14 years (Patti et al., 2020; Dive et al., 2020; Giovannoni et al., 2021; Yamout et al., 2020). The remaining five experts (36%) would consider an additional course of CladT in a stable patient as part of an individual treatment decision or as part of a clinical study (Table S2). Such decisions are not simple and may be influenced by a patient's own preferences and clinical parameters, such as the presence of high-risk prognostic factors, in addition to aspects of individual management, for example the feasibility of frequent clinical and MRI assessments. MS is a chronic disease with no known cure and waiting for DA to recur may increase the accrual of further irreversible disability, especially for those patients who presented with highly active disease, who were subsequently stabilised by a DMT. This is complicated further in that around half of disability worsening in RMS occurs independently of relapses, arguing for a more vigilant and proactive approach (Lublin et al., 2022). A recent analysis of clinical trial data from 1935 patients enrolled in CLARITY, CLARITY-EXT and ORACLE-MS applied a machine-learning approach to predict future DA (Basu et al., 2022). Five criteria were used to assess DA, of which 3-month sustained EDSS progression was the most informative. In this model, the probability of future DA decreases with the increasing number of treatment weeks, up to 4 weeks, confirming the optimal CladT dose of 3.5 mg/kg given over 2 years. Similarly, increasing counts of new combined unique active lesions and new T1 hypointense lesions raise the predicted probability of future DA. Indeed, Giovannoni et al. (2022) observed that the percentage of patients with NEDA-3 numerically decreases as the bridging interval between CLARTY and CLARITY-EXT exceeded 48 weeks. Therefore, there is a delicate balance between 'wait and see' and proactive intervention to limit future progression (Pandit, 2019; Smith et al., 2017).

In the event of continued treatment with CladT, a minimum of one additional course of CladT was recommended with the possibility of a second course depending on clinical response (Q6). This contrasts with a recent consensus publication, in which the approved two courses were

recommended, unless there were safety considerations (Meuth et al., 2022). The longer-term safety of CladT and any potential cumulative effects of additional courses is of interest, however, there were few real-world data reporting such outcomes (Q5). While articles reporting alternative formulations of cladribine were excluded from the SLR, longer follow ups with subcutaneous (s.c.) cladribine are available and may provide some reassurance on the long-term safety. In a retrospective, observational study of 52 patients with RMS who received off-label s.c. cladribine over a 5–20-year follow-up period, 80% of patients received additional courses (Rejdak et al., 2021). Increased cumulative doses of s.c. cladribine over a prolonged time period suggest that repeated courses of the drug can keep MS stable and are generally well tolerated by patients (Rejdak et al., 2021). In a real-world cohort of 242 MS patients who received two courses of s.c. cladribine, 18 received a third course of treatment; 7/18 patients received CladT as their additional course, and 11/18 received an additional course of s.c. cladribine (Allen-Philbey et al., 2022). The decision to administer a third course was based on: MRI activity (8 patients), clinical relapse (2 patients), both MRI activity and clinical relapse (5 patients), elevated CSF neurofilament levels (2 patients) and lack of compliance with first treatment (1 patient). The time between completing the first cladribine treatment (~Month 12) to the beginning of the additional treatment course was 37.2 months (Allen-Philbey et al., 2022). A longer-term safety follow-up of these patients would be of great interest and relevance.

Integrated safety analyses from the CladT clinical programme showed no increased rates of malignancies or infections in patients receiving higher and additional courses of CladT during the clinical studies (Cook et al., 2019; Leist et al., 2020). Chronic immunosuppression may increase the risk of infections and certain malignancies, and, with maintenance therapies, the risk of AEs increases with cumulative exposure to the drug (Boyko and Boyko, 2018). However, with selective IRTs, such as CladT, the majority of risk is front loaded due to the dosing schedule. The risk of the most frequent AEs (e.g. lymphopenia) is greatest following treatment administration (Boyko and Boyko, 2018; Giovannoni and Mathews, 2022). From the clinical programme of CladT, it has been observed that lymphopenia does not lead to an increased risk of common or severe infections, with the exception of herpes zoster (Giovannoni et al., 2010, 2018). These data together offer some insights regarding long-term safety of additional courses; however, more real-world cohort and registry data are needed.

Studies including MAGNIFY-MS (NCT03364036), CLASSIC-MS (NCT03961204), CAMELOT-MS (NCT04997148), CLARION (EUPAS24484), CLOBAS (ACTRN12619000257167), CLIP-5 (BfArM ID 7623), and country-specific cohorts will provide further data and evidence regarding the use of CladT. Of particular interest is the phase IV MAGNIFY-MS study, which evaluates whether early changes in immune cell phenotypes correlate with MRI-detectable disease control, possibly providing further evidence to support management decisions in the first 2 years of CladT treatment. CLIP-5 will investigate the efficacy and safety of CladT continuation at Year 5. Additionally, CLOBAS will evaluate CladT safety and efficacy over 6 years, offering continuation of therapy in the third year, based on DA after the initial two courses. The results are keenly anticipated.

Limitations of this review include the scarcity of real-world data for some questions, particularly those relating to long-term follow up with CladT, and those where additional courses have been administered. It is 5 years since EU approval of CladT, and more real-world studies with longer follow-up periods are expected to be published in the coming months. Another limitation is that since most eligible studies were in abstract form, detailed information on methodology, patient management and outcomes were lacking in many cases.

5. Conclusion

RWE for the long-term use of CladT in the treatment of RMS is increasing, but gaps in knowledge remain. In the absence of evidence, expert opinion and experiences are useful to provide guidance on topics and questions that occur in daily clinical practice. Further clinical and real-world studies are required to investigate whether additional courses of CladT are effective and well tolerated, in addition to providing information on which patients are likely to need and/or benefit from further treatment.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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