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REVIEW

Holistic, Long-Term Management of People with Relapsing Multiple Sclerosis with Cladribine Tablets: Expert Opinion from France

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ABSTRACT

Cladribine tablets (CladT) has been available for therapeutic use in France since March 2021 for the management of highly active relapsing multiple sclerosis (RMS). This high-efficacy disease-modifying therapy (DMT) acts as an immune reconstitution therapy. In contrast to most high-efficacy DMTs, which act via continuous immunosuppression, two short courses of oral treatment with CladT at the beginning of years 1 and 2 of treatment provide long-term control of MS disease activity in responders to treatment, without the need for any further pharmacological treatment for several years. Although the labelling for CladT does not provide guidance beyond the initial treatment courses, real-world data on the therapeutic use of CladT from registries of previous clinical trial participants and patients treated in routine practice indicate that MS disease activity is controlled for a period of years beyond this time for a substantial proportion of patients. Moreover, this clinical experience has provided useful information on how to initiate and manage treatment with CladT. In this article we, a group of expert neurologists from France, provide recommendations on the initiation of CladT in

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DMT-naïve patients, how to switch from existing DMTs to CladT for patients with continuing MS disease activity, how to manage patients during the first 2 years of treatment and finally, how to manage patients with or without MS disease activity in years 3, 4 and beyond after initiating treatment with CladT. We believe that optimisation of the use of CladT beyond its initial courses of treatment will maximise the benefits of this treatment, especially early in the course of MS when suppression of focal inflammation in the CNS is a clinical priority to limit MS disease progression.

Keywords: Multiple sclerosis; Cladribine tablets; Disease-modifying therapy; Holistic management

Key Summary Points
Cladribine tablets (CladT) acts as an immune reconstitution therapy in contrast to most high-efficacy DMTs, which act via continuous immunosuppression
The labelling for CladT does not provide guidance beyond the initial 4 years following the initiation of treatment, but real-world data indicate that MS disease activity is controlled for a period of years beyond this time for a substantial proportion of patients
Clinical experience has provided useful information on how to initiate and manage treatment with CladT
In this article, a group of expert neurologists from France provide recommendations on the initiation of CladT, how to switch from existing DMTs to CladT, and how to manage patients during the first 2 years of treatment and in years 3, 4 and beyond after initiating treatment with CladT

INTRODUCTION

Recent years have seen the introduction of multiple new high-efficacy disease-modifying therapies (DMTs) for the management of relapsing multiple sclerosis (RMS) [1]. This development has increased the potential for personalised management of the individual patient with RMS, while simultaneously adding complexity to the selection of the most appropriate management regimen. When considering either the initiation of a new DMT or a switch to a different DMT, the neurologist must both consider the present situation (e.g. the patient's MS disease history, comorbidities, lifestyle and personal preferences) and anticipate possible future developments to ensure an optimal balance of efficacy and safety over time (e.g. based on prognostic factors or whether the patient plans on starting a family). Finally, the physician must be ready to intervene in the event of unacceptable MS disease activity to amend the regimen and re-establish control of the disease.

DMTs for the management of MS can be categorised in various ways. For example, platform DMTs, such as interferons, glatiramer acetate, teriflunomide, dimethyl fumarate (DMF) or diroximel fumarate, are products with either no (in the case of immunomodulators) or a low level of immune suppression with moderate efficacy, while high-efficacy DMTs usually act via continuous immunosuppression [2, 3]. The escalation model of therapy for RMS often involves initial prescription of a platform agent, followed by a switch to a high-efficacy DMT if MS disease activity is not controlled [4]. The early use of high-efficacy DMT is increasingly common, especially for patients presenting with highly active MS. The European labelling (SmPC) for some high-efficacy DMTs supports their use as the first-line treatment for RMS, without the need to demonstrate high disease activity. The increasing choice of DMTs now available and their different clinical characteristics and mechanisms of action have provided greater opportunity for individualisation of patient care while increasing the complexity facing the physician and patient when agreeing the most appropriate DMT regimen to adopt.

Immune reconstitution therapy (IRT) is another high-efficacy therapeutic choice for the management of RMS. IRT involves administration of short and distant courses of treatment, followed by a period free of MS disease activity that can persist for years in most treated patients [2, 5]. Healthcare professionals in some countries, including France, have limited experience in applying this relatively new modality of care to their patients with RMS. Cladribine tablets (CladT) is the principal available IRT in France (where the authors practise medicine). Use of other agents which may act via an IRT-like mechanism is restricted in France because of safety concerns (alemtuzumab [6]); they are little used in practice (mitoxantrone or autologous hematopoietic stem cell transplantation) or are given continuously to produce a state of continuous immunosuppression (anti-CD20 agents, such as ocrelizumab, ofatumumab or rituximab [5]). Figure 1 summarises the posology of CladT from its European labelling [7, 8]. Current guidelines have provided a practical framework for the therapeutic use of CladT over the first 2 years of treatment [9], and data from real-world studies have shown generally similar efficacy and safety outcomes in real-world studies compared with the earlier randomised trials [10–17]. Follow-up of patients treated with CladT beyond 4 years after the first administration was limited at that time, and today we have few real-world studies that follow patients for this long (described below); moreover, it is notable that while giving explicit instructions for the initiation of CladT, like other DMTs, the label provides no guidance on how to manage the patient beyond the duration of the registration trial.

We published recommendations on the place of IRT (effectively CladT, as described above) in 2023, focusing on the types of patients with RMS who might be considered for this therapy [9], supported by a further comprehensive review of the safety and tolerability of CladT [8]. As real-world therapeutic experience with CladT has increased, the longer-term therapeutic profile of this agent becomes better understood. In this review, we update and expand our previous recommendations on the holistic management of people with RMS treated with CladT, from the initial prescription to long-term treatment beyond years 3 or 4 of therapy.

DATA SOURCES

The content of the article is based on the clinical experience of the authors (expert clinical neurologists based in France), local guidelines (for some aspects of holistic management such as treatment switches and MRI follow-up) and information published in the clinical literature. Published articles for review were identified via a search of PubMed and EMbase, as well as data presented at recent international congresses, focusing on the therapeutic use of CladT, especially beyond the 2nd year of treatment. We checked that data presented in abstracts had not been superseded by full-length publications: where this was not so we included contributions to congresses within our evidence base to capture the most up-to-date clinical information. The searches confirmed that published data on the use of CladT in people with MS (PwMS) are limited largely to 4 years of treatment, with few data for treatment beyond year 5. The recommendations presented here for long-term treatment with CladT were developed at a series of meetings where consensus was achieved through discussion (no formal consensus procedure was used) and represent the experts' positions on best clinical practice while waiting for new data to ensure optimum patient care.

This review article is based on previously conducted studies and the clinical expertise of the authors in treating patients with RMS. No new clinical studies were performed by the authors. No patient-specific efficacy or safety data were reported; therefore, institutional review board (IRB)/ethics approval was not required.
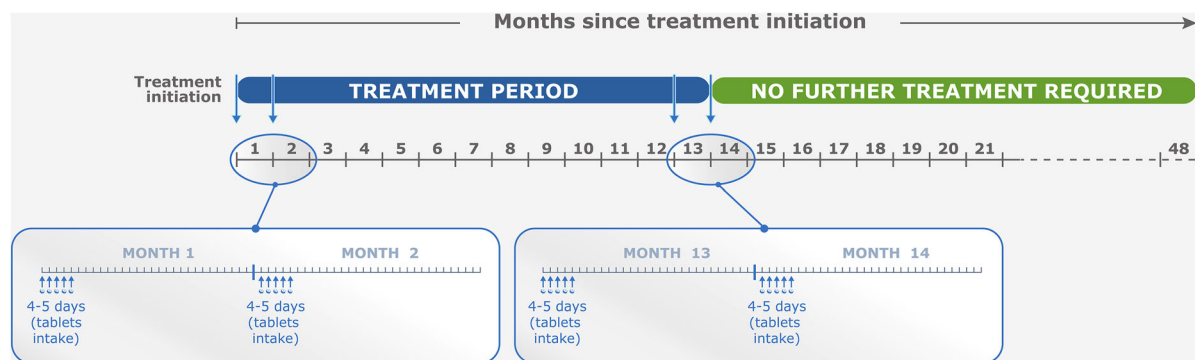
Fig. 1 Overview of cladribine tablet posology for relapsing multiple sclerosis patients. [a]Cladribine tablets is given as two treatment courses 1 year apart [7]. Inset shows details of one treatment course: blue arrows show treatment days at the beginning of month 1 and month 2 (5 treatment days are shown for each month, but in practice this could be 4 or 5 days, depending on body weight). [b]European Summary of Product Characteristics (SmPC). Compiled from information presented in the European SmPC for cladribine tablets [7] and aadapted here from reference [8] under the Creative Commons Attribution-Non Commercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0)

INITIATION OF TREATMENT WITH CLADRIBINE TABLETS FOR THE MANAGEMENT OF RELAPSING MULTIPLE SCLEROSIS

General Principles Relating to the Prescription of Immune Reconstitution Therapy for RMS

A key aspect of the treatment consultation is to match the DMT with the patient's preferences, expectations and lifestyle [18]. First, CladT is a high-efficacy DMT, as shown in the pivotal CLARITY study and in real-world studies [19, 20], and is therefore suitable for patients with high MS disease activity. Successful administration of IRT results in a lack of continuous treatment beyond the initial treatment courses, which may be attractive to patients who find the administration, monitoring and side effects of continuous immunosuppression burdensome or adherence to continuous treatment regimens challenging (see below). A period of (potentially) years without continuous administration also provides an opportunity for the person with MS to conceive and deliver a child if they are prepared to wait out the labelled 6-month post-treatment washout period (for CladT) before a pregnancy should occur [21]. Intention to pursue a family in the near future may be a reason to switch between a DMT that is contraindicated during pregnancy to IRT [21].

Finally, CladT is a well-tolerated oral therapy, which may be important for some patients and may help to support adherence to the treatment regimen (fingolimod and ponesimod are also administered orally every day, but other high-efficacy DMTs are monoclonal antibodies administered by injection or infusion). Indeed, for a responder to CladT, the issue of adherence disappears once the Year 1 and 2 courses of treatment have been taken, as no regular administrations of treatment are needed. Support programmes are available in a number of countries to optimise adherence to the year 2 course, which is high in real-world practice [22, 23]. Data from the MSBase registry showed that PwMS have a longer time-to-treatment discontinuation with CladT compared to other oral therapies [24]. Consistent with these observations, scores from validated instruments to measure quality of life and patient satisfaction are generally high during treatment of RMS with CladT [25–27].

Cladribine Tablets as the First Disease-Modifying Therapy

The European SmPC for CladT contains a therapeutic indication "for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features" [7]. While it refers to the results of the CLARITY study to describe the clinical efficacy of CladT in RMS, including the post hoc analysis in patients with high disease activity prior to the study [28], there is no clear definition of "highly active" RMS in the SmPC for CladT. Similarly, there is no clear consensus for defining "highly active relapsing RMS" in the clinical literature [18]. In addition, the absolute lymphocyte count (ALC) needs to be "normal" (not defined further) before the first dose of CladT [7].

We support the pragmatic approach outlined in the SmPC for the DMT-naïve patient as it is consistent with the ultimate goal of management or RMS, which is to prevent the accumulation of disability. A number of observational studies have demonstrated lower long-term progression of disability in subjects who received high-efficacy DMT earlier rather than later [4, 29–34]. Early administration of CladT fits with the need to suppress focal inflammation early in the clinical course of RMS, as this is a key driver of MS disease progression at this time [18].

The criteria for prescribing CladT as initial therapy may become broader in future as the evidence base for this approach increases, including from real-world studies [20, 35]. Such a change in approach would be consistent with increasing use of high-efficacy DMTs at earlier stages of the evolution of MS compared with the standard escalation approach where a switch to a high-efficacy DMT occurs only after the patient has been exposed to further MS disease activity [36], including for treatment-naïve individuals [37]. The early intensive therapy approach has been shown in observational studies to protect patients from clinical and radiological MS events, progression of disability or conversion to secondary progression of MS [32, 38–40]. Current European guidance for the management of RMS does not restrict the choice of DMT to a platform agent for a patient with early, highly active MS disease activity [9].

SWITCHING TO CLADRIBINE TABLETS FROM OTHER DISEASE-MODIFYING THERAPIES

Switching Between DMTs: General Principles

It is rational to switch to a high-efficacy DMT when MS disease activity has recurred, including clinical or radiological activity. Similarly, a lateral switch or switch to a high-efficacy DMT may also be considered if unacceptable tolerability or safety concerns have arisen during treatment with a platform DMT. The short-term goal is to suppress inflammation in the CNS, as this contributes to relapses and disease progression primarily early in the course of MS [41–44]. There is substantial evidence that earlier rather than later use of high-efficacy DMTs improves long-term disability outcomes in populations with RMS, as described above. However, "disability" is too often conflated with "motor physical handicap", i.e. EDSS score progression. More research is needed to define the effects of different aspects of MS progression, such as cognitive function, mood/affect and patient-reported outcomes relating to fatigue, difficulties at work and impact on daily life [45–48].

Prevention of reactivation or exacerbation of MS disease activity is paramount when switching between DMTs, so that a switch must achieve a balance between prompt restoration of protection against relapses while preserving safety. The Société Française de la Sclérose en Plaques (SFSEP) published guidance in this area in 2021 [49]. Switching from a platform therapy (interferons, glatiramer acetate, teriflunomide or DMF) can be done immediately, without the need for a washout period between treatments. The same guidance should be considered for diroximel fumarate, which was not available at time the SFSEP guidance was published. One caveat to this approach is the need to ensure that absolute lymphocyte count is $> 800/mm^3$

after withdrawal of DMF, as persistent lymphocytopenia has been observed for as long as 5 years after withdrawal of this agent, with the possibility of low absolute lymphocyte counts being erroneously attributed to the effects of the subsequent treatment [50–52]. A 3-month washout period should follow withdrawal of ocrelizumab, and a 6-month washout period should follow withdrawal of mitoxantrone, based on local SFSEP guidelines in France [49]. Fingolimod and natalizumab differ from other high-efficacy DMTs in that withdrawal of these agents has been observed to provoke severe and potentially disabling reactivations of MS disease activity, often beginning 6–8 weeks (fingolimod) or around 3 months (natalizumab) following the cessation of treatment [53–58]. The SFSEP therefore recommend that a washout period of 1 month should follow withdrawal of these DMTs to facilitate prompt reestablishment of therapeutic cover with the new DMT. Moreover, as per SmPC recommendation, a baseline MRI scan should be performed up to 3 months before initiating CladT initiation to exclude the presence of progressive multifocal leukoencephalopathy (PML) or other serious infections before starting treatment, especially when switching from another DMT [7].

Figures 2 summarises recommendations for switching from an existing DMT to CladT, and these are explained below.

Switching to Cladribine Tablets from a Platform DMT

We support the recommendation of the SFSEP in that treatment with CladT can begin immediately after withdrawal of interferon, glatiramer acetate, DMF or teriflunomide. While the European Summary of Product Characteristics for CladT [7] states that ALC should be $> 1000/mm^3$ before initial administration of CladT, this will be problematic for some patients previously receiving DMT, especially DMF and fingolimod as per above. We suggest that minimising the delay before establishing the new treatment is important. Our recommendation, based on expert opinion, is that it is preferable to initiate CladT when ALC is $> 800/mm^3$ and that the individual patient's level of MS disease activity should be considered

carefully before delaying the switch. We note that this same consideration would apply to the prescription of any new DMT and not only CladT.

Switching to Cladribine Tablets from an Anti-CD20 Agent

Ocrelizumab has a dosing interval of 6 months and we recommend that CladT should be started 3–6 months after the last dose (also based on local SFSEP guidance [49]) to ensure no loss of effectiveness of DMT. Ofatumumab is administered monthly and CladT may be initiated no later than time of the next scheduled dose after cessation of ofatumumab.

Switching to Cladribine Tablets from Leucocyte Anti-trafficking Agents (natalizumab or S1P modulators)

A washout period post-natalizumab of up to 1 month is recommended to reduce the risk of disease reactivation. The onset of action of CladT is rapid (as little as 2 months [59]); thus, minimizing the wash-out period should minimise the risk of rebound MS disease activity. As mentioned previously and as per label recommendations [7], it is important to conduct an MRI scan during this period and prior to CladT initiation to rule out any early or asymptomatic PML. Minimising the washout period duration rather than waiting for an ALC threshold is preferable when switching from an S1P modulator: we recommend starting CladT as soon as 2 weeks after withdrawing fingolimod and 1 week after withdrawing ponesimod (although further data on the short-term recovery of ALC after discontinuing these agents would be helpful to identify a time when sufficient lymphocytes are likely to have been released to support the mechanism of IRT after withdrawing these agents). For completeness, we do not provide a recommendation on the use of ozanimod because it is neither available for prescription nor reimbursed in France.

It is important to remember that patients will seek to switch their DMT from these agents for a range of reasons, including JCV positivity on natalizumab (high risk of rebound), for MS disease activity unrelated to this, or to avoid
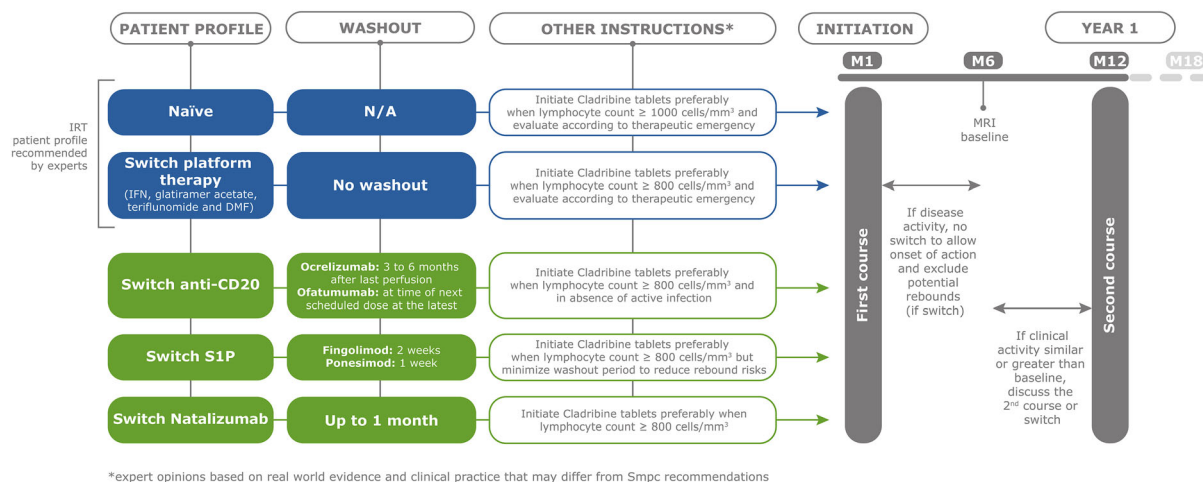
Fig. 2 Overview of the expert opinion on the management of patients treated with cladribine tablets at time of initiation according to patient profile regarding prior DMT and follow-up recommendation during 1st year of treatment. *Expert opinion based on real-world evidence and clinical practice that may differ from recommendations in the European Summary of Product Characteristics [7]. *DMF* dimethyl fumarate, *IFN* interferon, *IRT* immune reconstitution therapy, *M1, M6*, etc., refers to months, *MRI* magnetic resonance imaging, *N/A* not applicable, *S1P* sphingosine-1-phosphate inhibitor(s)

PATIENT MANAGEMENT AFTER INITIATION OF CLADRIBINE TABLETS

Year 1 (Period of Administration of Cladribine Tablets, Fig. 2)

The nadir for ALC after a course of CladT occurs at about 8 weeks in year 1, with gradual recovery thereafter for most patients [60]. ALC should be monitored 2 and 6 months after initiation of treatment, with continued monitoring if ALC is < 500/mm³, according to the drug's European label [7]. Data from the MAGNIFY study registry showed that the onset of action of CladT is rapid, with significant reduced risk of MRI lesions occurring from the 2nd month of treatment onwards, and efficacy continues to increase over the first 6 months [59]. Accordingly, a rebaselining MRI is useful 3–6 months after starting CladT and a routine annual MRI

continuous treatment, as discussed elsewhere in this article. The physician's knowledge and experience are therefore essential for achieving the best overall treatment decision.

thereafter. No data are available to provide guidance on whether to include a spinal cord MRI, and this will be done or not according to practice at local centres.

It is important to note that the full efficacy of CladT is achieved only when the second (year 2) course of treatment has been given [61–64]. Accordingly, physicians must use their clinical judgement as to whether the appearance of some MS disease activity in year 1 represents a serious reactivation of MS disease activity that requires a treatment switch, e.g. if the activity is similar to or higher than that seen on the previous DMT. Residual MS disease activity may persist for some months beyond the switch to CladT. This situation does not necessarily require a switch from CladT to another high-efficacy DMT before administration of the year 2 course of CladT. In the CLARITY study, 14% of patients demonstrated MS disease activity after the first course of CladT, but 61% of these patients demonstrated no further MS disease activity in year 2, following the second course. Real-world evidence suggests that most patients who report MS disease activity during year 1 of treatment do not switch to an alternative DMT, a systematic review of real-world studies with

Table 1 Summary of published cohorts reporting patients treated with cladribine tablets who discontinued or switched treatment during year 1, prior to the second course of cladribine tablets

References	Country	No. of patients	No. of discontinuations or switches [N (%)]
[65]	Canada	111	0
[66]	Italy	60	1 (1.7)
[67]	Spain	85	5 (5.9)
[68]	Spain	88	2 (2.3)
[69]	Czechia	436	12 (2.8)
[70]	USA	616	6 (1.0)
[71]	Germany	270	3 (1.1)
[72]	Sweden	140	5 (3.5)
[73]	United Arab Emirates	88	1 (1.1)
[14]	Finland	179	4 (3)
[74]	International	610	1 (0.2)
[75]	International[a]	782	31 (4.0)
[76]	Portugal	182	13 (7.1)
Totals:		3628	87 (2.4)

[a]MSBase registry. Compiled from data presented in reference [20]. References [14] and [76] were updated to reflect articles included in reference [20] as an abstract but subsequently followed by publication of a full paper

CladT in 3628 people with MS [20] showed that only 2.4% of patients discontinued or switched away from CladT in the 1st year of treatment (Table 1) [14, 65–76]. The phenomenon of MS disease reactivation after withdrawing an S1P inhibitor or natalizumab is a different phenomenon to residual MS disease activity during the time needed for the efficacy of CladT to build. The physician's knowledge and experience is key to decipher residual disease activity from disease reactivation requiring a modification of the therapeutic strategy, as mentioned above.

Beyond the Second Course of Cladribine Tablets (Fig. 3)

It is important to note that the lack of need for continuous drug administration with an IRT in a patient who responds to treatment does not equate to a lack of need for general clinical management. An MRI for rebaselining followed by annual MRI is recommended, as per recommendations from the Observatoire Français de la Sclérose En Plaques (OFSEP). In addition, clinical monitoring may continue annually or every 6 months, depending on local practice and whether residual MS disease activity is occurring (see below).

The CLASSIC-MS registry is following up patients originally enrolled in the CLARITY study and its extension. An analysis of these data ($N = 435$) showed that 63% of patients did not use a subsequent DMT for at least 4 years after the second course of CladT, 48.0% showed no evidence of disease reactivation, and 33% met both of these criteria [77]. More than half of the CLASSIC-MS population (53%) did not receive another DMT during a median follow-up of 10.9 years since the last dose of CladT. Data from the CLARINET-MS registry showed that 66.2% and 57.2% were relapse free at 36
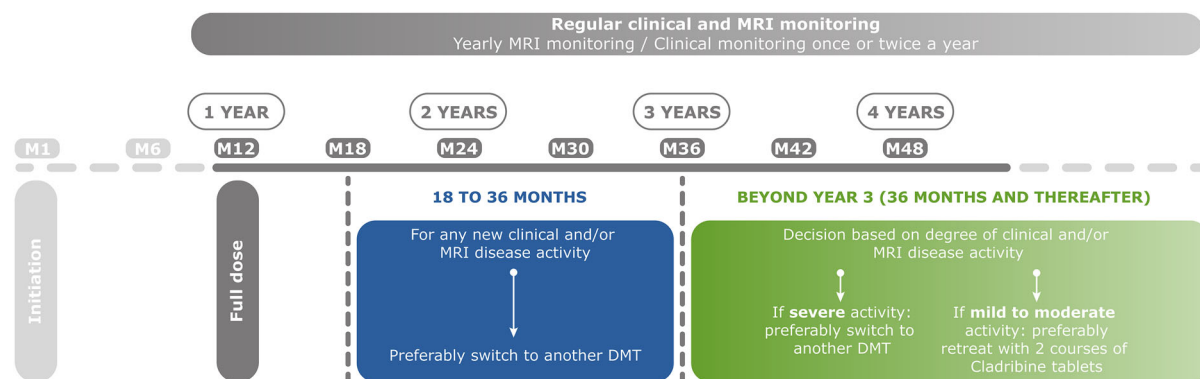
Fig. 3 Overview of expert opinion on patient management after taking a full dose of cladribine tablets, year 1 and beyond. *DMT* disease-modifying treatment, *M6, M12*, etc., refers to months, *MRI* magnetic resonance imaging

and 60 months, respectively, after the last dose of cladribine tablets (i.e. about 4 years and 6 years after the end of treatment, respectively) [78]. Long-term suppression of MS disease activity beyond the 4-year period studied in the CLARITY trial and its extension is therefore clearly possible. One real-world study showed that 26% of people with MS treated with CladT demonstrated recurrent MS disease activity during a median follow-up period of 4.5 years and that this was associated with higher MRI activity at baseline and receipt of a lower than indicated dose for the second course of CladT [79]. Another registry-based study found that 74% of a Clad-T-treated population achieved NEDA-2 during year 4 of treatment of a population with highly active MS [80].

There is no need for retreatment with CladT for a patient with no MS disease activity in years 3, 4 and beyond. The reappearance of MS disease activity should not be tolerated from 6 months after the second course of CladT onwards when lymphocytes will have largely repopulated and immune reconstitution should have occurred. As shown in Fig. 3, any MS disease activity in the latter part of year 2 or in year 3 from the initiation of treatment should prompt consideration of a switch to an alternative high-efficacy DMT such as monoclonal antibodies, which may present a higher level of efficacy [81]. Beyond year 3, the appearance of severe disease activity should lead to considering a switch to another high-efficacy DMT, while patients with mild-to-moderate MS

disease activity at this time may be candidates for treatment with a further two annual courses of CladT. Switching to another DMT from CladT is straightforward in years 2 and 3, as lymphocytes will have recovered from the second course, and no washout period is required before initiating a new DMT. These recommendations are largely aligned with expert opinion from Germany [82].

Data regarding retreatment after year 4 remain limited, especially regarding the implications for safety of additional courses of CladT, and the current evidence base does not support systematic retreatment after year 4 for patients, even with poor prognostic factors. Further real-world data are required to address this question: the CLIP-5 and CLOBAS observational cohorts will evaluate the efficacy and safety of CladT at 5 and 6 years following initial administration, respectively [20]. Biomarkers are needed to assist prediction of longer-term outcomes in patients treated with CladT (and, indeed, for all DMTs). Data from the MAGNIFY-MS cohort will examine the relationships between early changes in immune cells and longer-term treatment outcomes in patients who received CladT for RMS [11]. Effects on memory B cells after CladT have emerged as an interesting potential early marker of efficacy in MAGNIFY-MS and elsewhere [83, 84]. Annual immunophenotyping to monitor memory B cells may therefore provide another predictive marker of future MS disease activity [85, 86]. CladT has been shown to reduce serum neurofilament light chain (sNfL),

a biomarker of axonal damage in MS, although further validation of this biomarker is needed to predict who may need re-treatment with CladT [87].

Other current (published in 2023) expert opinion for the management of CladT-treated people with MS who develop moderate MS disease activity after year 4 recommends either 1–2-year courses of CladT or an alternative high-efficacy DMT [88–92]. All stress the importance of a thorough, individualised risk/benefit consideration before deciding on the future management policy at this time.

PREDICTING FUTURE MS DISEASE ACTIVITY OR PROGRESSION OF DISABILITY

Regarding the considerations on switching DMTs above, it would be ideal if patients at risk of needing treatment intensification could be identified on the basis of their clinical presentation. Scores derived from clinical and radiological findings in patients with multiple sclerosis (e.g. based on the MAGNIMS or RIO cohorts, or others such as the Risk of Ambulatory Disability score) have been used to predict the future occurrence of disease activity during treatment with interferonβ or glatiramer acetate [93–95] to predict progression of disability during treatment with interferons [96–99], glatiramer acetate [99], natalizumab [99], teriflunomide [100], DMF [101] or an S1P modulator [99–101] or to predict the likelihood of a sub-optimal response following a switch from platform DMTs to fingolimod or natalizumab [102]. Another study used a range of these scores to predict future disability after 1 year of treatment with various DMTs [103]. An elevation in the level of sNfL is another emerging clinical biomarker for an imminent deterioration in clinical status in populations with MS [100]. These approaches should be validated in different populations of patients with relapsing multiple sclerosis, for example those managed in different countries with different healthcare systems [104].

CONCLUSIONS

The use of CladT is now established within the management of RMS, particularly earlier in the course of therapy when suppression of focal inflammation in the CNS is a clinical priority to limit MS disease progression. Continued follow-up of patients previously enrolled in randomised evaluations of CladT, together with real-world data from routine clinical practice, has provided new information on the efficacy, safety and optimal application of this treatment. Nevertheless, current published data are almost completely limited to 4 years of treatment, with only a handful of data available beyond year 5. In this article, experts in the management or RMS in France have addressed this gap in knowledge and provide practical recommendations on the management of people with MS with CladT through 4 years and beyond.

A previous publication has explored the profiles of people with MS who may respond well to IRT in general and CladT in particular (essentially those relatively early in the MS disease process where focal inflammation is a key driver of disease progression, for whom IRT/CladT may delay the need for continuous immunosuppression) [9]. However, we have been clear that there is a lack of hard clinical evidence to support the management of a patient with MS disease activity 4 years after starting CladT, and this is why we have sought to communicate our expert opinion in this article. As described above, the choice faced by a neurologist for a CladT-treated person with MS under these circumstances is effectively to re-treat with CladT or to switch to another high-efficacy DMT such as monoclonal antibodies. Lack of information on the relative consequences of this choice reflects another important gap in our evidence base and a necessary limitation of our approach. As a result, we have not sought to provide specific recommendations on which road to take. CladT and other high-efficacy DMTs are not equivalent: all of these drugs vary in their efficacy, safety and tolerability profiles and management decisions for patients with RMS must depend ultimately

on the individual clinical presentation of the patient together with their personal needs and preferences. Our recommendations here provide pragmatic guidance on the use of CladT for a range of patient types within this context.

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Declarations

Ethical Approval. This review article is based on previously conducted studies and the clinical expertise of the authors in treating patients with RMS. No new clinical studies were performed by the authors. No patient-specific efficacy or safety data were reported; therefore, institutional review board (IRB)/ethics approval was not required.

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