

Practical Guidance on the Use of Cladribine Tablets in the Management or Relapsing Multiple Sclerosis: Expert Opinion from Qatar

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Abstract: The increasing availability of high-efficacy disease-modifying therapies (DMT) for the management of relapsing multiple sclerosis (RMS) has increased the potential for individualised patient management but has added complexity to the design of treatment regimens. The long-term application of immune reconstitution therapy (IRT) is supported by an increasing database of real world studies that have added important information on the long-term safety and efficacy of this approach. Cladribine tablets (CladT) is an IRT given as two annual short courses of treatment, following which a majority of patients then demonstrate no significant MS disease activity over a period of years. Whether, and how, to treat patients beyond the first two years of treatment remains a matter for debate, as clinical evidence accumulates. We, a group of neurologists who manage people with RMS in Qatar, provide our expert consensus recommendations on the application and long-term management of CladT therapy based on our experience with treatment in the last 5 years. These include pragmatic recommendations for people with MS disease activity in years 3 and 4 (ie up to four years following first dose of CladT), and for people with or without MS disease activity in subsequent years. We believe our recommendations will help to ensure the optimal application of CladT-based IRT, with the potential benefit for the patient of achieving prolonged periods free of both MS disease symptoms and the burden of regular applications of immunosuppressive DMT.

Keywords: multiple sclerosis, disease-modifying therapy, cladribine tablets, Qatar

Introduction

The management of relapsing multiple sclerosis (RMS) has been transformed in recent years by the introduction of a number of new, high-efficacy disease-modifying treatments (DMTs).¹ Some of these are given continuously to suppress aspects of immune function (including natalizumab, ocrelizumab, and S1P inhibitors).² Alternatively, immune reconstitution therapies (IRTs, currently represented by cladribine tablets [CladT] and alemtuzumab) are given as two short pulsed courses of treatment one year apart.^{2,3} There is no requirement for regular treatment between these courses, nor for further treatment for years afterwards in patients without further MS relapse activity.^{2,3}

Each of the high-efficacy DMTs have distinct efficacy, tolerability, safety and administration profiles. This has increased choice of high-efficacy DMTs has expanded the prospects for personalised care, but also introduced complexity into the design of a regimen for an individual patient with RMS.^{4,5} Moreover, the evidence base supporting the use of the newer agents is expanding rapidly, especially with regard to real world experience.^{6,7} The authors, a group of neurologists who care routinely for patients with RMS in Qatar, provided expert recommendations on the management of RMS in Qatar in 2020.⁸ The purpose of this article is to provide an update with recommendations specifically on the

therapeutic use of CladT in people with RMS, focussed mainly on identifying the most appropriate group of patients to be considered for this treatment.

Characteristics of Multiple Sclerosis in Qatar

All patients with RMS are assessed initially at the Hamad General Hospital, the main tertiary centre for MS care in Qatar. Survey data have demonstrated a medium-to-high prevalence of MS in Qatar, with an over representation of females that is typical of most countries (Box 1).⁹ The average level of disability was relatively low at diagnosis of MS, with a median Kurtzke Expanded Disability Status Scale (EDSS) value of 2, indicating minimal impairment of a single functional system.¹⁰ Other data showed that the radiologic presentation tended to be more severe than in neighbouring countries, however. The prevalence of MS has increased by 45% in Qatari residents between 2010 and 2017.

Clinical Experience with Cladribine Tablets in Qatar

Real World Data

No randomised trial has compared CladT with placebo and/or another DMT in a specifically Qatari population. However, data on the effects of this agent in our population are available from retrospective real-world evidence presented recently at the 2022 meeting of The European Committee For Treatment And Research In Multiple Sclerosis.¹¹ Forty-nine people with MS (94% had a diagnosis of RMS) received CladT, of whom 32 received both courses of CladT and were followed up for a mean of 32 months. Treatment with CladT (compared with baseline, ie before treatment) was associated with higher proportions of subjects who were relapse-free (81% vs 25%) or free of gadolinium-enhancing MRI lesions (75% vs 38%). The annual relapse rate (ARR) was reduced from 0.97 at baseline to 0.08 after treatment. Radiologic evidence of MS disease activity was observed in 8 subjects during the first year of treatment, but in only a single subject after the second course. Almost all (31/32, 97%) were free of confirmed 3-month EDSS progression at study end.

The most common all-cause adverse event (AE) in the safety population (all 49 subjects who received CladT) was Covid-19 infection (24%); all cases were mild and none required hospital care. Five subjects (1.5%) developed Grade 3 lymphocytopenia (there was no Grade 4 lymphocytopenia). Other AEs were upper respiratory tract infections (n = 3, 6%) and a single case (2%) of each of oral candidiasis, herpes zoster, and urinary tract infection. Thirty-one patients (63%) did not report any AE.

Safety of Cladribine Tablets in Qatar Vs Elsewhere

The purpose of this section is to compare our clinical experience with CladT in Qatar with experience elsewhere. However, we will not describe the efficacy and tolerability/safety profiles of CladT in detail in this article, as these have been reviewed comprehensively already in the clinical literature.^{12–14} Briefly, the principal side-effect associated with CladT is transient lymphocytopenia. Levels of B lymphocytes (CD19+) are reduced markedly and reach a nadir by about 6 months after each treatment course and recover slowly thereafter. T-cells (CD4+ or CD8+) are affected less than B lymphocytes, and average T-cell counts do not fall below the normal range; recovery of T-cells proceeds more slowly.

The pivotal evaluation of CladT in people with RMS occurred in the 2-year CLARITY study and its 2-year extension phase.^{15,16} Grade 3 lymphocytopenia (absolute lymphocyte count [ALC] 200–500 mm⁻³) was a relatively common finding in

Box 1 Multiple Sclerosis in Qatar

Prevalence:	93 (95% CI: 83 to 105)/100,000 population (medium-to-high prevalence) Female: male ratio 1.73:1
Clinical features:	Relatively low median EDSS score (=2) at presentation Preponderance towards sensory (65%) and visual (45%) symptoms, vs less common presentation with motor (43%), cerebellar (32%), brain stem (27%), bladder or bowel (10%), or spinal cord (14%) symptoms Relatively mild disability (see above) but more severe radiologic presentation vs neighbouring countries

Notes: Abstracted from data presented in references 8 and 9.

Abbreviation: EDSS, Kurtzke Expanded Disability Status Scale.

that study (24.9% of patients, and 0.7% developed Grade 4 lymphocytopenia [$<200 \text{ mm}^{-3}$]). The much lower incidence of Grade 3 (and absence of Grade 4) lymphocytopenia in our study is probably due to a change in the posology of CladT following the CLARITY study. A rigid schedule of administration of CladT was employed in CLARITY, such that lymphocytes had not recovered in some patients by the time of the year 2 treatment course. The labelling for CladT was changed, based on that experience, so that a further 6 months can be allowed for lymphocytes to recover before giving the second course.¹⁷ This is the practice that we follow in Qatar, and the updated approach appears to be effective in reducing the risk of higher-grade lymphocytopenia.¹²

The other relatively common safety/tolerability issue with CladT is the emergence of opportunistic infections.¹² The sporadic appearance of herpes zoster and oral candidiasis is typical of this, and can be minimised by appropriate screening for latent infections and vaccinating where required.² Overall, no new or noteworthy safety concerns emerged from our real-world study, compared with published evidence.

Head-to-head clinical trials comparing high-efficacy DMTs are lacking, although most meta-analysis have suggested that the efficacy of Clad T is broadly comparable with that of other high-efficacy DMTs in terms of suppressing relapses, limiting disability progression or promoting the state of “no evidence of disease activity”.^{13,18–22} Moreover, CladT seems to be more effective in reducing relapse rates patients with higher vs lower disease activity.^{18,23} Figure 1 shows our expert opinion on the safety and efficacy of CladT and other DMTs used in the management of RMS.

Recommendations on the Role of Cladribine Tablets in the Management of RMS in Qatar

Table 1 summarises our recommendations for the management of MS, and these are also discussed briefly below.

Newly-Diagnosed Patients with Relapsing Multiple Sclerosis

The term, “newly-diagnosed” with RMS, should be used with caution when considering a new therapeutic regimen: this population is likely to contain people with mild MS disease activity for some time before a formal diagnosis, and also people who have presented for diagnosis with significant MS disease activity. Accordingly, a personalised approach is indispensable here, considering the patient’s history and whether there are risk factors for MS disease progression, such

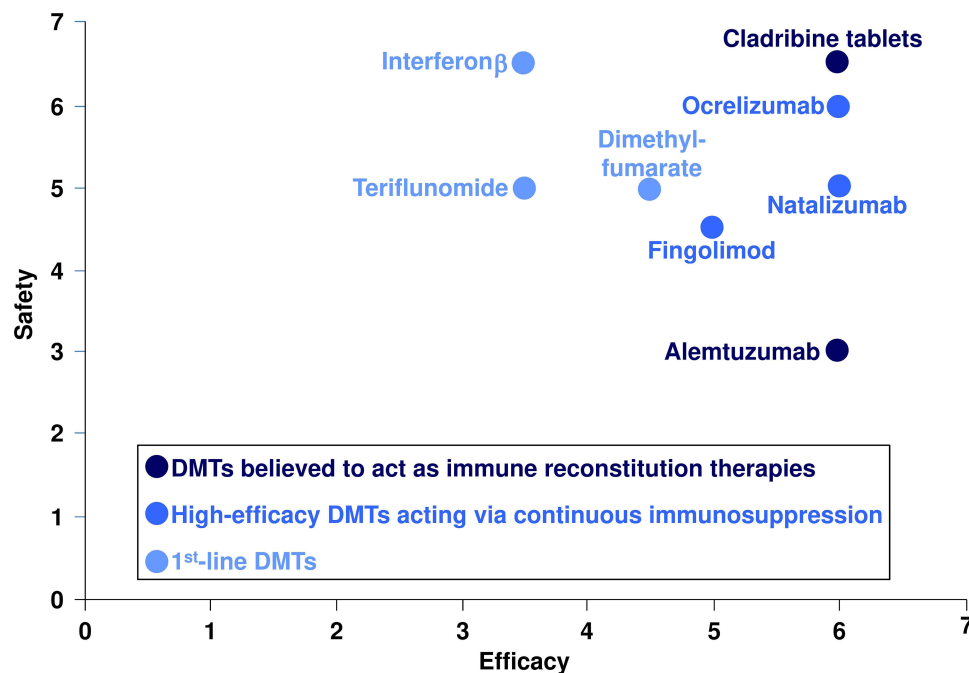


Figure 1 Consensus ratings of the efficacy and safety of disease-modifying therapies (DMTs) used in the management of relapsing multiple sclerosis. Expert neurologists (the authors) rated safety and efficacy on a Likert scale of 1 (least favourable) to 7 (most favourable). Average ratings are shown here.

Table 1 Summary of Recommendations

Newly-diagnosed MS	This is a heterogeneous group of patients: consider carefully individual histories, MS disease activity and prognostic factors for poor long-term MS outcomes 75–90% of patients with active MS ^a are likely to be suitable for initial management with cladribine tablets. All patients with highly active MS ^a are likely to be suitable for initial management with cladribine tablets. The remaining 10–25% of patients with low-risk, mild MS presentations are suitable for the escalation approach starting with a first-line DMT.
Switchers from 1st-line DMTs	Consider cladribine tablets for patients switching from a 1st-line DMT
Switchers from high-efficacy DMTs	No consensus: consider individual patient circumstances and preferences.
Years 3 and 4 of cladribine tablets	No need for re-treatment in the absence of MS disease activity (continue to monitor as usual) Retreat with 2 courses of cladribine tablets in the event of moderate MS disease activity ^b Retreat with 2 courses of cladribine tablets or switch to an alternative high-efficacy DMT in the event of significant MS disease activity ^c
Beyond year 4 of cladribine tablets	No need for re-treatment in the absence of MS disease activity (continue to monitor at longer intervals) Retreat with 2 courses of cladribine tablets in the event of moderate MS disease activity ^b Retreat with 2 courses of cladribine tablets or switch to an alternative high-efficacy DMT in the event of significant MS disease activity ^c

Notes: ^aSee text for definitions. ^b≤3 MRI lesions with or without a clinical relapse. ^c>1 relapse, a disabling relapse, or a high number of T2 MRI lesions. Based on expert opinion.

Abbreviations: DMT, disease modifying therapy; MS, relapsing multiple sclerosis.

as older age, spinal, infratentorial or cortical lesions, oligoclonal bands, frequent early relapses, early progression of disability, and lesions affecting motor function, among others.^{24–28}

We suggest that the level of MS disease activity is more useful for identifying patients who need earlier intervention with a high-efficacy DMT such as CladT. US²⁹ and European¹⁷ labelling for CladT and other high-efficacy DMTs employs terms such as “active” and “highly active” MS. These are not defined, however, and a recent consensus statement from the Gulf that included senior neurologists from Qatar among its authorship discusses this issue and provides recommendations.³⁰ Briefly, according to this classification, patients with “active MS” are those with one relapse in the last year, or two relapses in the last 2 years, but do not have poor prognostic indicators; those with “highly active” MS are those with at least two relapses in the previous year and more than nine T2 lesions, or more than one gadolinium-enhancing lesion without an impact on EDSS. A further category of “rapidly evolving severe RMS” have had at least two disabling relapses, with residual disability, or with MRI lesions in strategic prognostic areas (spinal cord, cerebellum, brain stem), or poor prognostic factors. Here, for conciseness, we consider the category of “highly active MS” to encompass the latter two groups.

The use of high-efficacy DMTs from diagnosis of MS (the “induction therapy” approach) remains controversial, despite accumulating evidence of superior long-term outcomes compared with the initial use of first-line DMTs (interferons, teriflunomide, dimethyl fumarate, glatiramer acetate where available) followed by escalation to high-efficacy DMTs when this approach proves insufficiently effective.^{1,31–36} We support the early intensive therapy approach: in our experience, prescription of CladT as the initial DMT after diagnosis of MS is suitable for 75–90% of patients with active MS and all patients with highly active MS.

It should be noted that patient preferences play an important role in the decision to start with treatment a high efficacy DMT. For example, people with MS tend to fear disability above all and are often likely to trade off perceived risks of a high-efficacy DMT for the prospect of improved long-term outcomes.^{37,38}

Treatment Switches

The results of scoring of perceptions of attributes of the therapeutic profile of CladT are shown in Table 2. There was strong support for early use of CladT in DMT-naïve patients, where suitable, as described above. Support was especially strong for use of this agent in patients with breakthrough MS disease activity on 1st-line DMTs. There was no consensus on the use of CladT for patients requiring a switch from other high-efficacy DMTs, consistent with observations that the efficacy of CladT

Table 2 Factors Influencing the Suitability of Cladribine Tablets for Different Subgroups of Patients with Relapsing MS

Attribute	Average Level of Agreement: 1 = No Support for Use of Cladribine Tablets, 7 = Strong Support for Use of Cladribine Tablets
Use of cladribine tablets in specific patient subgroups:	
DMT-naïve patients	6
Patients switching from 1st-line DMTs	7
Patients switching from other high-efficacy DMTs	4.5
Attributes of cladribine tablets:	
Reduces relapse rates	6.5
Reduces MRI activity	6
Good tolerability	7
Good long-term safety	5.5

Note: Based on expert opinion.

Abbreviation: DMT, disease modifying therapy.

and other high-efficacy DMTs is comparable.^{20,39} Patient preferences will be again important here, as some patients may prefer the potential of the IRT approach to deliver years free of active treatment for responders to therapy (see below).²

There was also strong agreement that CladT effectively suppresses clinical and radiologic MRI activity, with a good tolerability profile.¹²

Long-Term Use of Cladribine Tablets

The CLARITY study and its extension demonstrated that two annual courses of CladT provided durable efficacy throughout the following two years. However, there is no definitive evidence base at this time to guide the management of patients with breakthrough MS disease activity during years 3 or 4 of CladT therapy, or for management beyond 4 years.

It is important that all patients are monitored carefully after treatment with CladT as part of their usual care, including annual MRI scans and periodic measurement of the EDSS, according to local practice. We see no need to re-treat a patient without evidence of MS disease activity during years 3 and 4, as per the label. There was strong support for re-treatment with CladT during this period in response to moderate MS disease activity (eg ≤ 3 MRI lesions with or without a clinical relapse). This is broadly consistent with expert consensus recommendations from southeast Europe which called for retreatment with CladT in years 3, 4 and beyond in the case of “minimal” MS disease activity, defined as 1–2 new lesions without clinical relapse, or “moderate” MS disease activity, defined as a single relapse with 3–4 MRI new lesions.⁴⁰ An international expert panel did not achieve a consensus of treatment of a patient with new MS disease activity in years 3 and 4, but supported an individualized choice between retreatment with CLadT or a switch to another high-efficacy DMT beyond year 4.⁴¹ It is less clear how to proceed in the face of more serious MS disease activity (eg >1 relapse, a disabling relapse, or a high number of T2 MRI lesions), and clinical judgement is required.^{40–42} For example, recent expert opinion from Germany on the management of CladT-treated patients beyond year 4 considered that either retreatment with CladT or a switch to another high-efficacy DMT is indicated in the presence of recurrence of MS disease activity, with the decision based on consideration of the time since the last treatment with CladT, the severity of the relapse(s), trends in the level of MS disease activity over time, and the frequency, nature and location within the CNS of new MRI activity.⁴² Taken together, these clinical findings can be used to assess whether the patient may benefit from retreatment with CladT or is a non-responder to this treatment.

Recommendations for managing patients treated with CladT beyond year 4 were similar. Patients without MS disease activity at this time can be followed up at longer monitoring intervals (eg 6-monthly clinic visits with 2-yearly MRI scans).

Conclusions

The potential benefits of successful prescription of an IRT are substantial in that responders to treatment do not require active treatment following the completion of the second annual course of treatment. Thus, patients who presented with high MS disease activity may be free of the twin burdens of MS-related symptoms and of the need for regular intakes of immunosuppressive DMTs for a period of years.^{43–49} Most high-efficacy DMTs are contraindicated in pregnancy, so that such a situation can be of particular benefit for patients who wish to pursue a pregnancy (as long as the 6-month washout period following the last dose of CladT is respected, as per the product label).^{2,17,50–52} Patients who adhere poorly to a regular regimen, a common issue in the management of RMS, may also benefit from the IRT approach.^{2,17,50,51,53} Finally, the monitoring burden associated with CladT is relatively light, compared with other (especially infusional) DMTs, which suggests greater convenience and a lower impact on clinic time and patients' usual activities, compared with some other high-efficacy DMTs.²

The recommendations summarized above are intended to support the practising physician in the application of CladT-based therapy, especially beyond the first 2 years of treatment, at which time the product label provides little or no support. Further revisions to these recommendations will be needed in future as the evidence base for the long-term use of CladT grows. Our recommendations and others^{40–42} emphasize the need for clinical judgment when faced with a patient with recurrent MS disease activity more than 2 years after the first course of CladT. The accrual of longer-term data on the therapeutic profile of CladT over time will help to answer important clinical questions, including which demographic and/or phenotypic subgroups of patients respond best to retreatment with CladT beyond years 3 and 4, and what level of clinical or radiologic MS disease activity recurrence supports or precludes successful retreatment.

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Disclosure

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