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Expert Opinion on the Use of Cladribine Tablets in Clinical Practice

Per Soelberg Sørensen[1], Diego Centonze[2], Gavin Giovannoni[3], Xavier Montalban[4,5], Daniel Selchen[5], Patrick Vermersch[6], Heinz Wiendl[7], Bassem Yamout[8], Hashem Salloukh[9] and Peter Rieckmann[10]

1. Danish Multiple Sclerosis Center, Department of Neurology, University of Copenhagen and Rigshospitalet, Copenhagen, Denmark; 2. Unit of Neurology and Neurorehabilitation, IRCCS Neuromed, Pozzilli (IS), Italy; 3. Queen Mary University of London, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK; 4. Department of Neurology, Neuroimmunology, Multiple Sclerosis Centre of Catalonia (Cemcat), Vall d'Hebron University Hospital, Pg. Vall d'Hebron, 119-129, 08035 Barcelona, Spain; 5. University of Toronto, Division of Neurology, St. Michael's Hospital, Toronto, ON, Canada; 6. Department of Neurology, CHU Lille, LIRIC-INSERM U995, FHU Imminent, University of Lille, Lille, France; 7. Department of Neurology, Institute of Translational Neurology, University of Münster, Münster, Germany; 8. Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut, Beirut, Lebanon; 9. Merck, Aubonne, Switzerland; 10. Hospital for Nervous Diseases, Medical Park Loipl, Bischofswiesen, Germany.

INTRODUCTION

- The evolving treatment landscape in relapsing MS (RMS) requires physicians to have a comprehensive understanding of the different disease modifying drugs (DMDs) in order to offer optimal care.[1]
- Treatment labels rarely provide specific, detailed information on real-life usage.
- Cladribine tablets (Mavenclad®) is a short-course oral DMD for use in MS, that preferentially reduces lymphocytes.[2, 3]
- In order to address some of the unanswered questions relating to the use of cladribine tablets, here we describe a consensus-based programme led by international MS experts with the aim of providing practical recommendations to support its use in real-life clinical practice.

METHODS

- The consensus programme was based on a multi-step modified Delphi methodology, which took place between April 2018 and April 2019.
- A Steering Committee (SC) of nine international MS experts led the programme. The SC in turn was supported by an extended faculty (EF, n=33) of practicing neurologists caring for MS patients. A total of 19 countries were represented in the programme. The role of the EF was to review available evidence, complete a questionnaire and finally vote on draft recommendations.
- The SC identified practical clinical questions concerning the use of cladribine tablets and prioritised the most important 11 questions to be addressed, categorised into six topics.
- A comprehensive literature review was performed for each question. The level of evidence was assessed and agreed by the SC.[4]
- A questionnaire was developed by the SC with draft answers based on available evidence from the literature review, combined with their expert opinion, where evidence was lacking. The questionnaire was completed remotely via an on-line platform by the EF.
- The results from the questionnaire were incorporated into draft clinical recommendations, which were then voted on by the SC and EF members.
- Consensus was achieved when ≥75% of respondents agreed in the range of 7–9 (on a 9-point scale).[5]

RESULTS

- In total, 47 recommendations were drafted by the SC and voted on. Consensus was achieved on 46 of these recommendations.
- The clinical questions and recommendations are provided in Tables 1–6 for the following 6 topics:
  1. The definition of highly active disease
  2. The patterns of treatment response in patients treated with cladribine tablets
  3. Management of patients with evidence of disease activity while being treated with cladribine tablets
  4. Infection risk and immune function in patients being treated with cladribine tablets
  5. Management of pregnancy planning and malignancy risk in patients being treated with cladribine tablets
  6. Treatment switching to and from cladribine tablets and monitoring considerations

TABLE 1. DEFINING HIGHLY ACTIVE DISEASE

Consensus recommendations	Strength‡	Level of consensus¶
Q1a. What patient baseline characteristics and activity metrics indicate highly active disease: • If patients are *treatment naïve*? (Level of evidence: moderate)		
Clinicians should consider the following activity metrics that may indicate highly active disease in a treatment naïve patient: • 1 prior clinical relapse in the last year AND evidence of subclinical MRI activity (Gd+ or new or enlarging T2 lesions) in a patient with poor prognostic factors (clinical, MRI or biomarker) OR • 2 or more clinical relapses in the last year, with or without MRI activity	8	88.2%
Q1b. What patient activity metrics indicate highly active disease and suitability for high efficacy treatment or escalation therapy: • If patients have had an appropriate course of *a DMD*? (Level of evidence: moderate)		
Clinicians should consider the following activity metrics that may indicate highly active disease, and suitability for high efficacy treatment or escalation therapy, in a patient who has had an appropriate course of another DMD:* • 1 prior clinical relapse in the last year with subclinical MRI activity (Gd+ or new or enlarging T2 lesions) OR • 2 prior clinical relapses in the last year without MRI activity OR • ≥1 Gd+ lesions or ≥ 2 new or enlarging T2 lesions in the last 12 months	8	88.2%

*A new baseline MRI scan should be taken into consideration. The timing of the re-baseline scan may vary depending on the treatment.

‡Strength of recommendation = median score on a 1–9 scale; ¶percentage of votes with 7–9 on a 9-point scale

TABLE 2: PATTERNS OF TREATMENT RESPONSE IN PATIENTS TREATED WITH CLADRIBINE TABLETS

Consensus recommendations	Strength‡	Level of consensus¶
Q2a. What are the patterns of treatment response with cladribine tablets? (Level of evidence: low)		
A complete or durable treatment responder to cladribine tablets is a patient with no evidence of significant clinical or radiological activity after completion of the full recommended cumulative dose.*	8	93.9%
In the absence of new disease activity in Year 3, 4, or beyond, a patient is not a candidate for treatment switch to another DMD.	9	97.0%
Q2b. What are the patterns of suboptimal response with cladribine tablets? (Level of evidence: low)		
A patient with worsening or unchanged disease activity during the first two years of treatment with cladribine tablets, should be considered as a putative non- or suboptimal responder and is a candidate for treatment with a high efficacy DMD.	8	84.8%

*A new baseline MRI scan should be taken into consideration.
- Refer to Question 1b for the threshold of clinical or radiological activity in a patient following an appropriate course of a DMD that indicates a suboptimal responder
- Refer to Question 1b for the threshold of clinical or radiological activity in a patient following an appropriate course of a DMD that indicates a suboptimal responder
- Refer to Question 10 for 'How to switch from cladribine tablets'

‡Strength of recommendation = median score on a 1–9 scale; ¶percentage of votes with 7–9 on a 9-point scale

TABLE 3: MANAGING PATIENTS WITH EVIDENCE OF DISEASE ACTIVITY WHILE BEING TREATED WITH CLADRIBINE TABLETS

Consensus recommendations	Strength‡	Level of consensus¶
Q3a. How would you manage a patient who has taken the first course of cladribine tablets but has evidence of new disease activity in Year 1? (Level of evidence: moderate)		
After the first treatment course of cladribine tablets in Year 1, a patient with disease activity less than pre-treatment levels, might not necessarily be an indication for treatment discontinuation.*	8	97.0%
Corticosteroids should be used to treat the relapse according to local guidelines. Clinicians may wait and monitor the patient and provide cladribine tablets at the beginning of Year 2 in order to allow the patient to receive the recommended cumulative dose.	9	97.0%
Q3b. How would you manage a patient who has worsening disease activity during the first two years of treatment with cladribine tablets? (Level of evidence: very low)		
During the first two years of treatment with cladribine tablets, a patient with increasing disease activity above pre-treatment levels, may be a candidate for a treatment switch to another high efficacy DMD.*	8	87.9%
Corticosteroids should be used to treat relapses according to local guidelines.	9	97.0%
Q4a. How would you manage a patient who has taken the indicated two courses of cladribine tablets but has evidence of new / reappearing disease activity only in Year 3–4? (Level of evidence: low)		
Clinicians should consider a switch to another high efficacy DMD in a patient with a complete but non-durable response to cladribine tablets with evidence of new / reappearing disease activity in Year 3–4.	7	60.6% NOT ACHIEVED*
Clinicians should consider treatment options and associated risks and discuss with the patient.	9	100%
Q4b. How would you manage a patient who has taken the indicated two courses of cladribine tablets but has evidence of new / reappearing disease activity only beyond Year 4? (Level of evidence: low)		
Treatment options for a patient with a complete but non-durable response to cladribine tablets with evidence of new / reappearing disease activity beyond Year 4 could include: • **Consideration of a switch to another high efficacy DMD after thorough risk / benefit analysis.** • **Consideration of re-initiation with cladribine tablets, after thorough risk / benefit analysis.** – Benefit of additional treatment with cladribine tablets in response to disease activity beyond Year 2 has not been investigated. The incidence of lymphopenia and other adverse events is increased with additional treatment in Year 3 or 4. Re-initiation of therapy after Year 4 has also not been investigated. • **Clinicians should consider treatment options and associated risks and discuss with the patient.**	8	97.0%

*Disease activity in the first 3–6 months of treatment with cladribine tablets may be a carry-over from a patient's prior treatment, especially for those switching from lymphocyte trafficking agents (fingolimod or natalizumab).
- Refer to Question 1b for the threshold of clinical or radiological activity in a patient following an appropriate course of a DMD that indicates a suboptimal responder
- Refer to Question 10 for 'How to switch from cladribine tablets'.

‡Strength of recommendation = median score on a 1–9 scale; ¶percentage of votes with 7–9 on a 9-point scale

*The reasons provided by the EF for not agreeing with this statement was that they would consider re-treatment with cladribine tablets in this instance. However, the SC did not recommend re-treatment in Year 3 or 4 since this has not been formally investigated in a clinical trial setting, in addition to the increased incidence of lymphopenia and other adverse events following additional cladribine tablets treatment in Year 3 or 4 in the CLARITY EXT study.

TABLE 4: INFECTION RISK AND IMMUNE FUNCTION IN PATIENTS BEING TREATED WITH CLADRIBINE TABLETS

Consensus recommendations	Strength‡	Level of consensus¶
Q5a. How are patients with severe lymphopenia on cladribine tablets managed? (Level of evidence: moderate/low)		
A patient with grade 3 or 4 lymphopenia on cladribine tablets may be at an increased risk of infection and should be actively monitored for signs and symptoms of infections. Clinicians should consider appropriate prophylactic treatment based on the individual patient's risk.	8	93.8%
A patient with grade 3 or 4 lymphopenia should be actively monitored for signs and symptoms particularly suggestive of herpes zoster. A patient should also be informed about the signs and symptoms of herpes zoster. If such signs and symptoms occur, anti-viral treatment should be initiated immediately.	9	96.9%
Q5b. Do patients with severe lymphopenia on cladribine tablets need anti-viral prophylaxis against herpes zoster? Which anti-herpes therapy should be used prophylactically? (Level of evidence: low)		
Initiation of anti-viral prophylaxis with a licenced anti-viral drug should be recommended in a patient with grade 4 lymphopenia.	8	84.4%
Initiation of anti-viral prophylaxis with a licenced anti-viral drug may be considered in a patient with grade 3 lymphopenia. Special consideration should be given to any patient at risk of herpes zoster infection such as elderly patients.*	8	75.0%
Anti-viral prophylaxis should be maintained until severity of lymphopenia is reduced.	8	83.9%
Vaccination with Shingrix may be considered for any patient at increased risk of herpes zoster infection (for example those with positive serum titres, age ≥50, previous herpetic exacerbations).	8	81.3%

*Grade 3 lymphopenia was more common in Year 2 of the CLARITY study, and duration of lymphopenia was longer. Zoster infection is more common in older patients.
The history of the patient should be taken into consideration including the patient age, prior duration of lymphopenia and previous infection with varicella zoster virus.
- Refer to Questions 6 and 7 for recommendations on vaccinations

Q6. What vaccinations are recommended as part of the de-risking strategy before patients are initiated with cladribine tablets? (Level of evidence: very low)		
Clinicians should review a patient's vaccination status before initiation with cladribine tablets and consult their local vaccination guidelines.	9	93.8%
Vaccination for varicella zoster virus is recommended in any antibody-negative patient prior to initiation of cladribine therapy.	9	96.9%
Q7. How do you manage vaccinations after treatment with cladribine tablets; inactivated component vaccines vs. live attenuated vaccines? (Level of evidence: low)		
Cladribine tablets should not be initiated within 4 to 6 weeks after vaccination with live or attenuated live vaccines.	9	100%
Any use of live attenuated vaccines should be avoided during treatment with cladribine tablets. Users should wait for the leukocytes / lymphocytes to return to normal wherever possible.	9	96.8%
If an inactivated component vaccination is essential for a patient, clinicians should wait for the lymphocyte levels to return to within the normal range.	8	77.4%
For certain multi-dose vaccinations, clinicians may consider giving the first dose of the vaccine 4–6 weeks before treatment initiation with cladribine tablets. Subsequent vaccine dose(s) should be given at a later date, after initiation with cladribine tablets, once lymphocyte counts have recovered.	8	93.5%
Q8. How should latent or active infections be managed before initiation of cladribine tablets? (e.g. positive PPD / Quantiferon test for TB, HPV [cervical screening], HBV/HCV test, PML) (Level of evidence: low)		
Cladribine tablets are contraindicated in a patient with HIV or an active chronic infection (e.g. Hepatitis B&C, VZV, Syphilis, TB, PML etc.), and a delay in initiation of cladribine tablets should be considered in a patient with an acute infection until the infection is fully controlled.* • In any case of infection (latent or active), a relevant specialist should be contacted (e.g. infectious disease, pulmonologist, hepatologist etc.). • The infection should be diagnosed, managed, and treated according to local guidelines.	9	96.8%
Screening for PML is recommended in any patient previously treated with natalizumab, particularly those who are JCV antibody positive, and a baseline MRI (within 3 months) should be performed before initiation of cladribine tablets. Additional CSF analysis should be considered.	9	83.3%

*Clinicians should consider a patient's prior treatment since those switching from a DMD associated with lymphopenia, may be at an increased risk from latent infections.

‡Strength of recommendation = median score on a 1–9 scale; ¶percentage of votes with 7–9 on a 9-point scale

TABLE 5: PREGNANCY PLANNING MANAGEMENT AND MALIGNANCY RISK IN PATIENTS BEING TREATED WITH CLADRIBINE TABLETS

Consensus recommendations	Strength‡	Level of consensus¶
Q9a. How should pregnancy planning be managed in patients on cladribine tablets? (Level of evidence: very low)		
Based on human experience with other substances inhibiting DNA synthesis, cladribine tablets could cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity. There is very limited pregnancy data from the clinical trial programme.	8.5	96.9%
Cladribine tablets are contraindicated and should not be administered during pregnancy. Subsequent courses of cladribine tablets may be delayed during this time.	9	100%
Breast-feeding is contraindicated during dosing with cladribine tablets and for 10 days after the last dose.	9	93.8%
Before initiation of treatment both in Year 1 and Year 2, women of childbearing potential and males who could potentially father a child should be counselled regarding the potential for risk to the foetus and the need for effective contraception for at least 6 months after the last dose of cladribine tablets.*	8	100%
Any unforeseen pregnancy within 6 months after the last dose of cladribine tablets is not necessarily an indication for a termination of the pregnancy. Any further administrations of cladribine tablets should, however, be discontinued immediately or delayed in this event. Patients should be counselled about potential risks to the foetus and referred to a high-risk pregnancy clinic.	9	96.9%

*It is currently unknown whether cladribine may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should add a barrier method during cladribine treatment and for at least 4 weeks after the last dose in each treatment year[2]

Q9b. Do cladribine tablets result in an increased risk of malignancy? (Level of evidence: moderate)		
Cladribine tablets may increase the risk of malignancies, as seen with other high efficacy DMDs. • There was a higher incidence of malignancies in clinical studies and long-term follow-up of patients treated with a cumulative dose of 3.5 mg/kg cladribine tablets compared with placebo,* however, when compared to a matched reference population, there was no evidence for an increased risk.**	8	86.7%
Clinicians should instruct patients to observe the standard guidelines for cancer screening.	9	100%
Cladribine tablets are contraindicated in patients with an active malignancy.	9	90.0%

*Included all studies that used cladribine tablets monotherapy, matching the recommended dose: CLARITY, CLARITY EXT and ORACLE-MS + follow-up in PREMIERE.
**The rate of malignancies observed with cladribine tablets during the clinical development programme in MS was similar to the expected rate in the GLOBOCAN reference population (8.00 observed events in the monotherapy oral cohort versus 8.27 expected events, respectively; SIR: 0.97 [95% CI 0.44, 1.85]). Non-melanoma skin cancer was excluded due to inconsistent reporting in GLOBOCAN. Data is adjusted for country of origin, age and gender.

‡Strength of recommendation = median score on a 1–9 scale; ¶percentage of votes with 7–9 on a 9-point scale

TABLE 6. TREATMENT SWITCHING TO AND FROM CLADRIBINE TABLETS AND MONITORING CONSIDERATIONS

Consensus recommendations	Strength‡	Level of consensus¶
Q10. When switching to cladribine tablets, what are the washout periods / baseline requirements for different DMDs? Are there any specific treatment classes that preclude cladribine tablets as a next switch?* (Level of evidence: very low)		
Switch decisions should be made after a thorough risk / benefit analysis.[1, 2]	9	100%
Due to a lack of clinical evidence for treatment switches in MS, caution should be taken in a patient who is switching from a prior treatment due to adverse events that may also occur with cladribine tablets.	9	90.0%
*Due to a lack of clinical evidence for treatment switches in MS, recommendations are based on individual treatment risks or carry-over risks.		
Glatiramer acetate / Interferon-beta • Possible treatment effects on **blood** (e.g. lymphopenia, leukopenia, thrombopenia), and/or **liver** and **kidney** parameters should have **subsided** • **Recommended safety interval:** none generally required	9	100%
Dimethyl fumarate • Possible treatment effects on the **differential blood count**, should have subsided following the last dose of dimethyl fumarate • Possible additional treatment effects on **blood** (e.g. severe lymphopenia), **liver/kidney** parameters should have **subsided** • **Recommended safety interval:** none generally required	9	93.5%
Teriflunomide • Possible treatment effects on the **immune** system and **liver** values should have subsided • **Washout** necessary – it must be documented that teriflunomide is **no longer detectable** in the **blood** • **Recommended safety interval:** normally around 4 weeks	8	90.3%
Fingolimod • Possible treatment effects on the **differential blood count**, should have subsided following the last dose of fingolimod. There should be no cytopenia. • Possible treatment effects on other **blood** parameters and **liver** values, as well as **vital signs**, should have subsided • **Recommended safety interval:** normally around 4 weeks	8	80.0%
Natalizumab • Possible effects on the **immune system** (e.g. lymphocytosis, cytopenia) should have **subsided** • **PML** should be **excluded** (e.g. MRI including FLAIR sequence immediately before start of treatment). A **CSF examination** including a **JCV-PCR** should be considered beforehand in patients with **positive JCV antibody status** and a **treatment duration of >12 months**) • **Recommended safety interval:** normally around 4–8 weeks	8	90.3%
Alemtuzumab • Possible treatment effects on the **immune system** (e.g. cytopenia) should have subsided (lymphocyte typing is optional e.g. T and B cells) • **Clinical** and **laboratory monitoring** (including platelets, creatinine, TSH and urine sediment) must be **continued for 4 years** following the last alemtuzumab infusion • **Recommended safety interval:** normally around 6–12 months	8	96.8%
Ocrelizumab • **Differential blood count** must be **ascertained** before treatment initiation (lymphocyte typing is optional e.g. CD19+ B cells) • Any treatment effects on the **immune system** (e.g. cytopenia) should have **subsided** • **Recommended safety interval:** normally around 6–12 months	8	93.1%
Q11. How do you switch from cladribine tablets? What DMDs can patients use after cladribine tablets? If the patient's lymphocyte counts have not recovered to LLN but a treatment switch is required, what is the recommended course of action? (Level of evidence: very low)		
Potential additive effects on the immune system should be considered when choosing subsequent DMDs following treatment with cladribine tablets.	9	93.5%
Treatment-specific effects on lymphocyte counts should have ideally subsided before switching from cladribine tablets.	8	100%
The waiting time is defined by the clinical need to switch. Cases of treatment non-response should be decided on an individual risk / benefit analysis.	9	100%
Caution is recommended in switching from cladribine tablets to natalizumab in any patient who is JCV antibody positive.	9	93.5%

‡Strength of recommendation = median score on a 1–9 scale; ¶percentage of votes with 7–9 on a 9-point scale

CONCLUSIONS

- **The recommendations described here are the collective opinions of a large international group of experts representing a wide geographical spread.**
- **They should provide practical, specific advice to all HCPs involved in the treatment and management of patients with MS, address gaps in existing guidance and ultimately improve care.**

DISCLOSURES

PSS has served on advisory boards for Biogen, Merck Healthcare KGaA, Novartis, Teva, MedDay Pharmaceuticals, and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck Healthcare KGaA, Teva, GSK, and Novartis; has received speaker honoraria from Biogen Idec, Merck Healthcare KGaA, Teva, Sanofi-Aventis, Genzyme, Celgene and Novartis. His department has received research support from Biogen, Merck Healthcare KGaA, Teva, Novartis, Roche, and Genzyme.

DC is an Advisory Board member of Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva. He is also the principal investigator in clinical trials for Bayer Schering, Biogen, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, Teva. His preclinical and clinical research was supported by grants from Bayer Schering, Biogen Idec, Celgene, Merck Serono, Novartis, Roche, Sanofi-Genzyme and Teva.

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XM has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, Excemed, MSIF and NMSS

DS has received grants and/or personal fees from Teva, Merck Serono, Novartis, Roche, Genzyme, Sanofi-Genzyme, Biogen Inc. and Bayer HealthCare.

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HW is a member of Scientific Advisory Boards/Steering Committees for Bayer Healthcare, Biogen Idec, Sanofi Genzyme, Merck Serono, Novartis, Roche, and Teva. He received speaker honoraria and travel support from Bayer Vital GmbH, Bayer Schering AG, Biogen, CSL Behring, EMD Serono, Fresenius Medical Care, Genzyme, Merck Serono, Omniamed, Novartis, and Sanofi Aventis and Teva. He received compensation as a consultant from Biogen Idec, Merck Serono, Novartis, Omniamed, Roche, and Sanofi Genzyme. He has received research supports from Bayer Healthcare, Bayer Vital, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, Sanofi US, and Teva Pharma as well as German Ministry for Education and Research (BMBF), German Research Foundation (DFG), Else Kröner Fresenius Foundation, Fresenius Foundation, Hertie Foundation, Merck Serono, Novartis, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (ISKF) Muenster, RE Children's Foundation.

BY has received honoraria for lectures and advisory boards from Bayer, Biogen, Genpharm, Genzyme, Merck-Serono and Novartis; and has received research grants from Bayer, Biogen, Merck-Serono, Novartis and Pfizer.

HS is an employee of Merck, Aubonne, Switzerland.

PR has received honoraria for lectures/steering committee meetings from Merck, Biogen Idec, Bayer Schering Pharma, Boehringer-Ingelheim, Sanofi-Aventis, Genzyme, Novartis, Teva Pharmaceutical Industries, and Serono Symposia International Foundation.

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