Poster No. DX71

Reduction of lymphopenia by cladribine tablets under re-treatment guidelines: a long-term follow-up analysis of patients in the ORACLE-MS study

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INTRODUCTION

- In the majority of patients, treatment with cladribine tablets induced mild, transient lymphopenia. In the CLARITY study 74.4% of patients receiving cladribine tablets 3.5 mg/kg and 55.0% receiving 5.25 mg/kg experienced a worst post-baseline lymphocyte count in the Grade 0–2 range.[1] Very few patients experienced Grade 4 lymphopenia (3.5 mg/kg: 0.7% only in Year 2, 5.25 mg/kg: 2.9% in Year 1 or 2). Lymphocyte measures occurred at study protocol–defined intervals.
- In the ORACLE-MS study in patients with a first demyelinating event, treatment with two short courses at the beginning of two consecutive years of cladribine tablets (total doses 3.5 mg/kg and 5.25 mg/kg) significantly reduced the risk of clinically definite multiple sclerosis (CDMS) compared with placebo.[2]
- Guidelines implemented in ORACLE-MS required that patients had to have at worst Common Terminology Criteria for Adverse Events (CTCAE) Grade 0 or 1 lymphopenia before receiving the second year's course of cladribine tablets.
  - If a patient had lymphopenia Grade 2 or higher, they discontinued from treatment and were followed up for safety

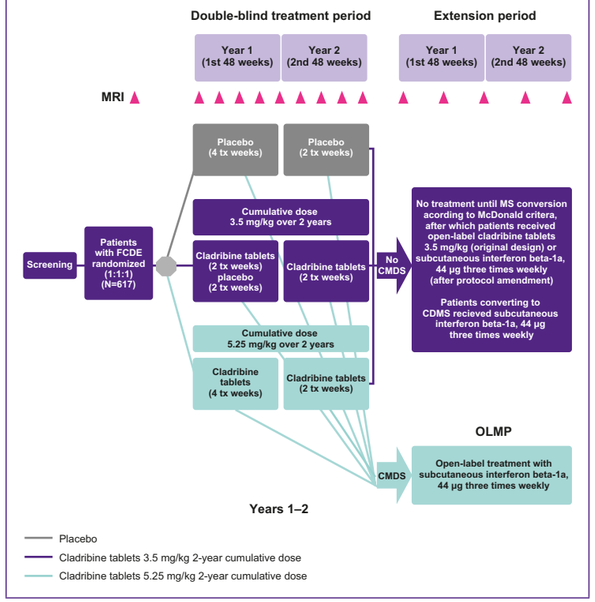
OBJECTIVE

- To assess severity and recovery from lymphopenia in the ORACLE-MS long-term follow-up (LTFU) among patients treated with cladribine tablets during the ORACLE-MS initial treatment period (ITP).

METHODS

- ORACLE-MS patients were aged 18–55 years with a first clinical demyelinating event within 75 days before screening, ⩾2 clinically silent lesions of ⩾3 mm on a T2-weighted brain scan, and an Expanded Disability Status Scale (EDSS) score of ⩽5.0.
- Patients were randomized (1:1:1) to placebo, cladribine tablets 3.5 mg/kg, or cladribine tablets 5.25 mg/kg of body weight (cumulative over 2 years).
- Eligibility for the re-treatment period (start of Week 48 to end of Week 96) required that all of the following laboratory hematological parameters, as measured at Week 44, were ⩾ the lower limit of Grade 1 according to the CTCAE: hemoglobin, leukocytes (total white blood cells), absolute lymphocyte count, absolute neutrophil count, and platelets. If a patient did not meet these re-treatment criteria, the patient was to be discontinued from treatment and followed-up for safety.
- Patients who did not convert to CDMS during the ITP were followed for safety and efficacy evaluations for up to 48 weeks after the end of the ITP (**Figure 1**).
- Patients in the LTFU did not receive any additional study medication during the LTFU, until conversion to MS according to the McDonald 2005 criteria, when they were treated with open-label cladribine tablets 3.5 mg/kg or with subcutaneous interferon β-1a 44 µg three times weekly.
- Patients who converted to CDMS during the LTFU period initiated treatment with subcutaneous interferon β-1a 44 µg three times weekly.
- We report the occurrence of lymphopenia in patients who completed the ITP following guidance for re-treatment with cladribine tablets and who received no further treatment during the LTFU.

Figure 1. ORACLE-MS study design



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CDMS, clinically definite multiple sclerosis; **FCDE**, first clinical demyelinating event; **MRI**, magnetic resonance imaging; **MS**, multiple sclerosis; **OLMP**, open-label maintenance period.

RESULTS

- During the ITP (up to 2 consecutive years), CTCAE Grade 3/4 lymphopenia occurred in 46 (22.3%) and 74 (36.3%) patients receiving cladribine tablets 3.5 mg/kg and 5.25 mg/kg, respectively, and 1 (0.5%) patient receiving placebo.
  - Grade 4 lymphopenia was limited to 3 patients; 1 (0.5%) treated with cladribine tablets 3.5 mg/kg and 2 (1.0%) treated with cladribine tablets 5.25 mg/kg.
- Following the ITP, 84 patients entered the LTFU and did not receive further treatment (**Table 1**).
- The patients were reflective of the baseline population of the ORACLE-MS study.
- In the placebo group, 47 patients completed the 2 years of the ITP and 14 of these entered the LTFU and received no further treatment.
- In the cladribine tablets 3.5-mg/kg group, 78 patients completed the 2 years of ITP, and 36 of these entered the LTFU and received no further treatment.
- In the cladribine tablets 5.25-mg/kg group, 65 patients completed the 2 years of ITP and 34 of these entered the LTFU and received no further treatment.

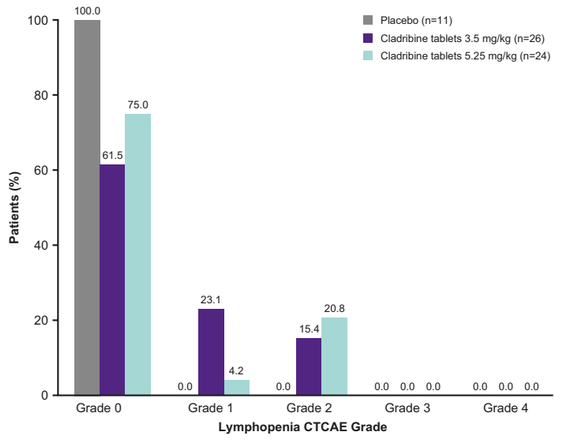
Table 1. Patients not treated at entry to LTFU

	Treatment group during the initial treatment period		
	Placebo (n=14)	Cladribine tablets 3.5 mg/kg (n=36)	Cladribine tablets 5.25 mg/kg (n=34)
CDMS conversion[a]	0 (0.0)	0 (0.0)	1 (2.9)
McDonald MS conversion[a]	0 (0.0)	0 (0.0)	1 (2.9)
Received cladribine tablets or subcutaneous interferon β-1a after conversion to CDMS or McDonald MS in LTFU	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued LTFU	14 (100.0)	36 (100.0)	34 (100.0)

CDMS, clinically definite multiple sclerosis; **LTFU**, long-term follow up; **MS**, multiple sclerosis.
[a]One patient converted to McDonald MS and then CDMS during the LTFU. Patients not treated at entry to LTFU entry = patients who completed the double-blind period without McDonald MS conversion and entered the LTFU.

- At LTFU baseline, none of the patients originally treated with cladribine tablets 3.5 mg/kg during the ITP had Grade 3/4 lymphopenia.
  - One patient originally treated with cladribine tablets 5.25 mg/kg during the ITP had Grade 3 lymphopenia at LFTU baseline.
- Four patients originally treated with cladribine tablets 3.5 mg/kg during the ITP had Grade 2 lymphopenia at LTFU baseline.
  - All of the patients originally receiving cladribine tablets 3.5 mg/kg during the ITP recovered to Grade 0 or 1 by LTFU Week 13 (the time of the first post-baseline scheduled visit).
- Some fluctuations were evident and some patients with Grade 0 or 1 lymphopenia at LTFU baseline had Grade 2 lymphopenia at later visits in the LTFU (**Figure 2**).

Figure 2. Worst post-baseline CTCAE grade in patients not treated during the LTFU



CTCAE, Common Terminology Criteria for Adverse Events; **LTFU**, long-term follow-up.

CONCLUSIONS

- **In ORACLE-MS, the occurrence of CTCAE Grade ⩾3 lymphopenia was dose-related. Grade 4 lymphopenia was observed in ⩽1% of patients.**
- **The re-treatment guidelines introduced in ORACLE-MS appeared to limit the occurrence of Grade 3/4 lymphopenia.**
- **Among the patients entering the LTFU who were originally treated with cladribine tablets 3.5 mg/kg during the ITP, none had Grade 3/4 lymphopenia at the LTFU baseline (the end of the ITP).**
- **Patients originally treated with cladribine tablets 3.5 mg/kg during the ITP who had Grade 2 lymphopenia at LTFU baseline recovered to Grade 0 or 1 by Week 13 in the follow-up period after the 2-year double-blind ITP.**

REFERENCES

1. Giovannoni G, *et al. N Engl J Med* 2010;362:416–26.
2. Leist T, *et al. Lancet Neurol* 2014;13:257–67.

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DISCLOSURES

TL is a consultant to EMD Serono, Teva Neuroscience, Biogen, Bayer, and Pfizer; and is involved in clinical trials sponsored by EMD Serono, Teva Neuroscience, Bayer, ONO, Novartis, Daiichi, and Acorda. **GC** has received consulting fees from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck, and Bayer Schering; lecture fees from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck Serono, Biogen Dompè, Bayer Schering, and Serono Symposia International Foundation; and trial grant support from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck, Biogen Dompè, and Bayer Schering. **MF** has received compensation from Bayer HealthCare, Biogen Idec, Chugai, EMD Canada, Genzyme, Merck, Novartis, Sanofi-Aventis, and Teva Canada Innovation. **BC** has served as an advisor or consultant for AbbVie Inc., Biogen, EMD Serono, Inc., Genzyme Corporation, MedImmune, Novartis Pharmaceuticals Corporation, Shire, and Teva Neuroscience, Inc. **PKC** has served as an advisor or consultant for AbbVie Inc., Accordant, Acorda Therapeutics, Bayer HealthCare Pharmaceuticals, Biogen, EMD Serono, Inc., Genentech/Roche, Genzyme/Sanofi, Novartis Pharmaceuticals Corporation, Teva Pharmaceuticals USA; and received grants for clinical research from Actelion Pharmaceuticals, Ltd., Biogen, Genentech/Roche, Novartis Pharmaceuticals Corporation, and Opexa Therapeutics, Inc. **H-PH** has received honoraria for consulting, membership of steering committees and advisory boards, and speaking at symposia – with approval of the Rector of Heinrich-Heine-University – from Bayer Healthcare, Biogen Idec, Genzyme, Medimmune, Merck Serono, Novartis Pharma AG, Teva, Sanofi-Aventis, Receptos, and Roche. **PV** has received honoraria and consulting fees from Biogen Idec, Sanofi, Bayer, Novartis, Merck, GSK, and Almirall; and research support from Biogen Idec, Sanofi, Bayer, and Merck. **ES** is an employee of Merck KGaA, Darmstadt, Germany. **DD** and **FD** are employees of EMD Serono, Inc.,* Billerica, MA, USA.

Cladribine tablets is currently under clinical investigation and has not yet been approved by any regulatory authority. Status: March 2017.

The ORACLE-MS study: NCT00725985

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