Effects of Cladribine Tablets on CD4+ T Cell Subsets in the ORACLE-MS Study: An Analysis of Lymphocyte Surface Markers

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INTRODUCTION

- The ORACLE-MS study demonstrated the efficacy of cladribine tablets 3.5 mg/kg cumulative dose over 2 years in patients with a first clinical demyelinating event.
  - Cladribine tablets significantly reduced the risk of conversion to clinically definite multiple sclerosis by 67%.[1]
- Evaluation of lymphocyte subtypes from patients in the cladribine tablets 3.5 mg/kg arm of the study showed that a transient median reduction of approximately 82% in CD19+ B cell count occurred by Week 13, with reconstitution from Week 24 to 48. CD4+ and CD8+ T cells were also reduced discontinuously (median reductions at Week 13 were approximately 55% and 44%, respectively), but had not fully returned to baseline at Week 48.[2]
- Cladribine tablets are proposed to be a form of immune reconstitution therapy, so longitudinal immune cell changes in this setting are of interest. Specifically, a prolonged decrease in pathological memory T cell subsets and/or the recovery of regulatory T cells may help to explain the durable clinical effect seen over 48 weeks after cladribine treatment.[3]

OBJECTIVES

- To examine effects on central and effector memory CD4+ T cells, and naturally occurring regulatory CD4+ T cells (nTreg cells) after the first administration of cladribine tablets in the ORACLE-MS[1] study.

METHODS

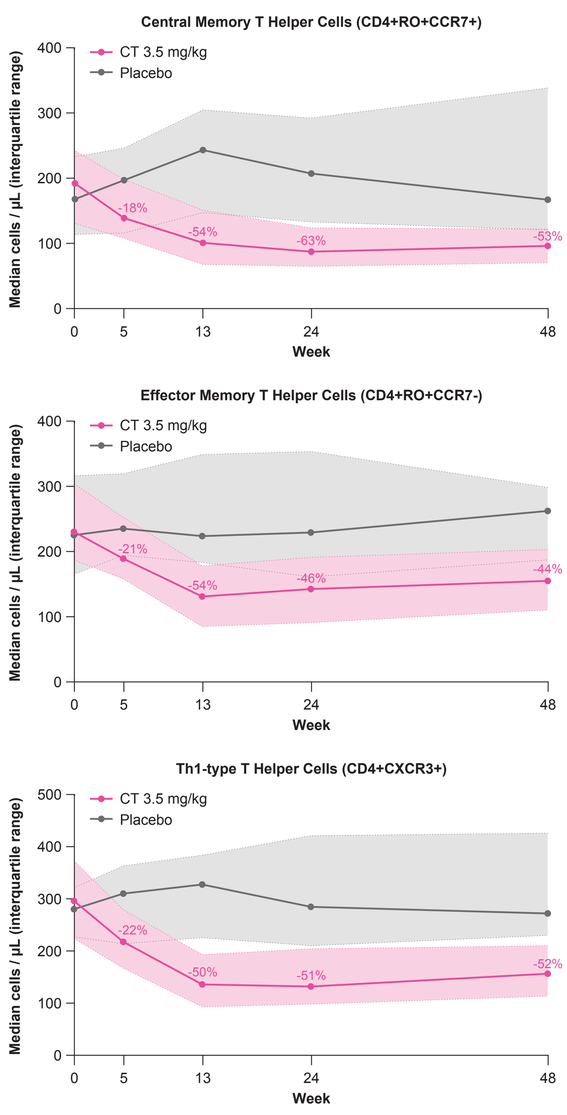
- A longitudinal (48 weeks) evaluation of peripheral blood lymphocyte subtypes was conducted for patients receiving the first course of cladribine tablets as part of the 3.5 mg/kg active treatment group of the ORACLE-MS study.
- Lymphocyte subset analyses were performed using flow cytometry to detect T lymphocytes expressing CD4+RO+CCR7+ (central memory), CD4+RO+CCR7- (effector memory), CD4+CXCR3+ (Th1-type), CD4+CD25+CD127- (nTreg cells), CD4+CD25+CD127-RA(HI)+ (naïve-like nTreg cells) and CD4+CD25+CD127-RA- (memory-like nTreg cells) lymphocyte surface markers (LSM).
- Blood samples for the LSM analysis were collected from a subset of patients, and immunophenotypes are reported at baseline and at Weeks 5, 13, 24 and 48.
- Changes in absolute cell numbers and changes in the relative proportion of CD4+ T lymphocyte subtypes were evaluated.
- Patients with at least one LSM assessment were included in this analysis.
- Patients who received interferon beta-1a had their LSM data censored from the time of starting interferon beta-1a.

RESULTS

Central Memory Cells, Effector Memory Cells, and Th1-Type T Cells

- The greatest median reductions from baseline in absolute cell numbers occurred at Week 24 for central memory cells (median -63% reduction from baseline), Week 13 for effector memory cells (median -54% reduction from baseline) and Week 24 for Th1-type cells (median -51% reduction from baseline), as shown in **Figure 1**.
- Timings of the lowest median absolute values do not necessarily correspond to the timings of the greatest median % reductions from baseline. This is the case with Th1-type cells.

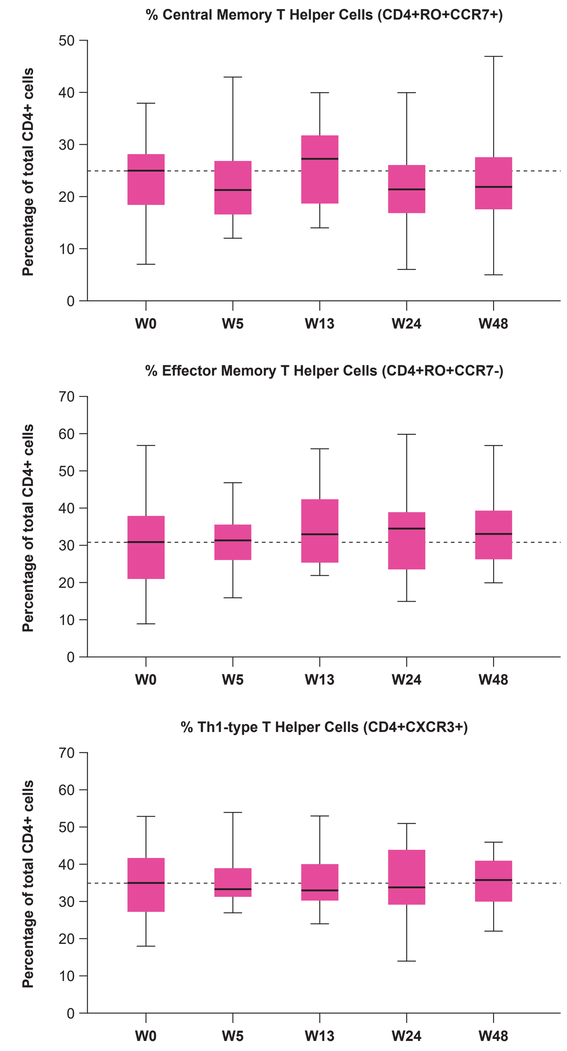
Figure 1. Median CD4+ Subtype Counts - Central Memory Cells, Effector Memory Cells, and Th1-Type Cells



Values are median absolute cell counts (Q1–Q3); percentages are median % change from baseline in CT-treated patients. N.B. Timings of the lowest median absolute values do not necessarily correspond to the timings of the greatest median % reductions from baseline.
CT, Cladribine tablets.

- At Week 48, similar or slightly increased levels of central memory cells, effector memory cells, and Th1-type cells were observed compared with levels at Weeks 13–24.
- The proportion of the central memory cells in total CD4+ cells was reduced by -5% and -9% at Weeks 24 and 48, but there was no reduction in the proportions of effector memory cells or Th1-type cells (**Figure 2**).

Figure 2. Temporal Profiles of CD4+ Subtype Proportions Over the First Dosing Year

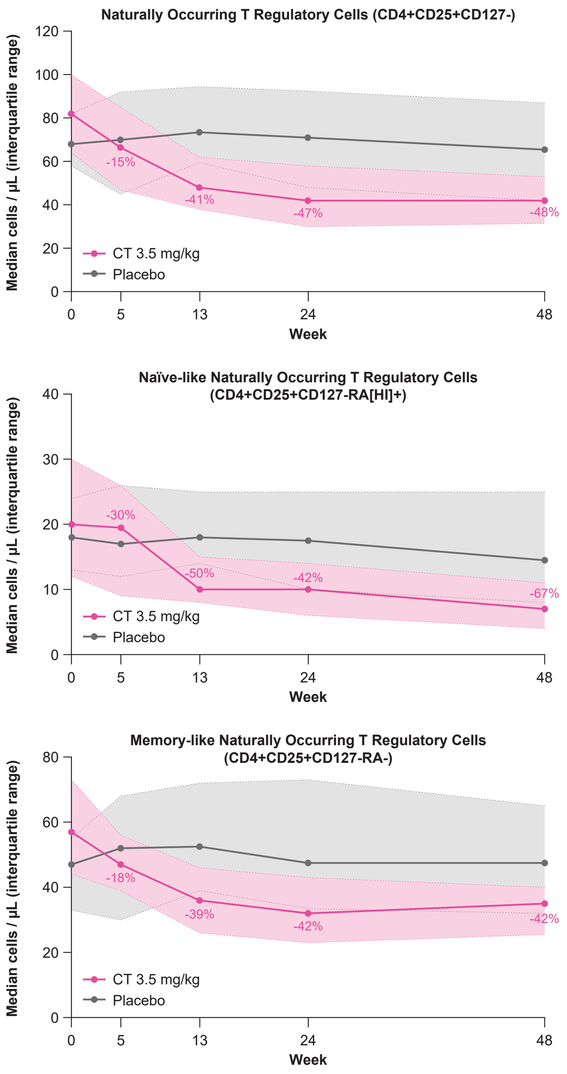


Lines within boxes represent median values, boxes represent Q1–Q3 values, whiskers represent minimum and maximum values, pink horizontal line represents median baseline percentage. **W**, Week.

Naturally Occurring Regulatory Cd4+ T Cells

- Absolute numbers of nTreg cells, naïve-like nTreg cells and memory-like nTreg cells in patients treated with cladribine tablets 3.5 mg/kg were decreased at Week 48 by median 48%, 67% and 42%, respectively (**Figure 3**).

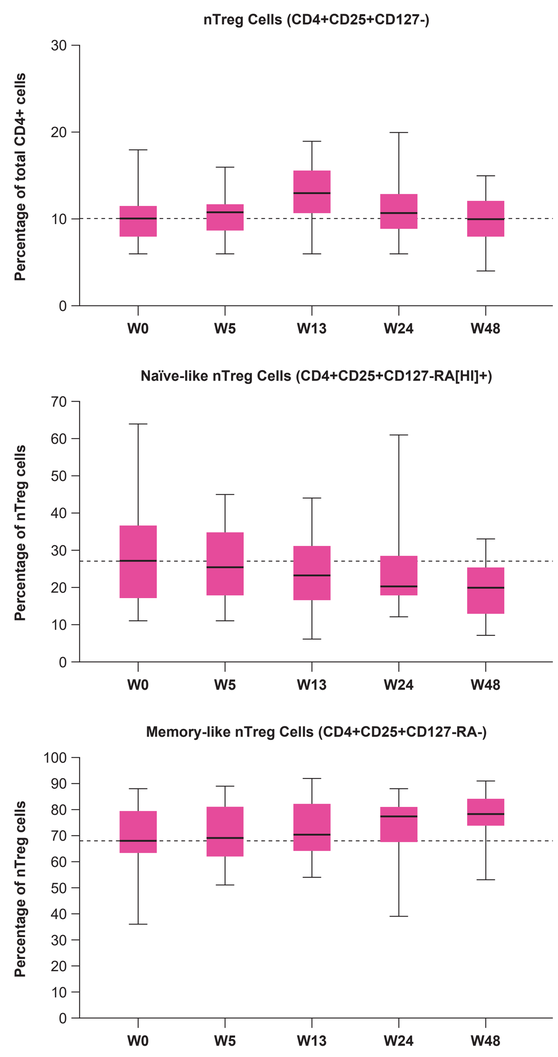
Figure 3. Median CD4+ Subtype Counts - Naturally Occurring Regulatory T cells



Values are median absolute cell counts (Q1–Q3); percentages are median % change from baseline in CT-treated patients. N.B. Timings of the lowest median absolute values do not necessarily correspond to the timings of the greatest median % reductions from baseline.
CT, Cladribine tablets.

- The nTreg cell proportion of CD4+ cells was similar at baseline and at Week 48 in patients treated with cladribine tablets 3.5 mg/kg (**Figure 4**).
- Naïve-like nTreg cells as a proportion of total nTreg cells were decreased up to Week 48 (median decrease from baseline in the proportion of memory-like nTreg cells was 36% at Week 48).
- Memory-like nTreg cells slightly increased up to Week 48 (median increase from baseline in the proportion of memory-like nTreg cells was 11% at Week 48).

Figure 4. Temporal Profiles of T Regulatory Cell Proportions Over the First Dosing Year



Lines within boxes represent median values, boxes represent Q1–Q3 values, whiskers represent minimum and maximum values, pink horizontal line represents median baseline percentage.
nTreg, naturally occurring T regulatory; **W**, week.

CONCLUSIONS

- **Maximal reductions from baseline were similar between T cell subtypes containing pathological memory cells (central and effector subsets) and proinflammatory Th1-type cells in patients receiving cladribine tablets.**
  - **Pathological memory cells and Th1-type cells had not recovered to baseline by Week 48, and the proportions of central memory T cells were slightly decreased at Weeks 24 and 48.**
- **nTreg cells were also decreased, but the proportion of memory-like nTregs showed a slight increase at Weeks 24 and 48.**
- **Taken together, the prolonged decrease in pathological memory T cells and Th1-type cells, combined with the recovery of regulatory memory T cell function, may contribute to the durable clinical effect of cladribine tablets.**

REFERENCES

1. Leist TP, et al. *Lancet Neurol.* 2014:13:257-267.
2. Stuve O, et al. ECTRIMS-ACTRIMS Paris 2017,#P690.
3. Giovannoni G, et al. *Mult Scler J.* 2017; doi 10.1177/1352458517727603.

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DISCLOSURES

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