Effects of Cladribine Tablets on B and T Lymphocytes and Natural Killer Cells in Patients with Early and Relapsing MS

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INTRODUCTION

• The efficacy of cladribine tablets 3.5 mg/kg (cumulative dose given in short courses annually for 2 years) has been demonstrated in patients with early multiple sclerosis in the ORACLE-MS study, and in patients with relapse–remitting multiple sclerosis in the CLARITY study maintained in the CLARITY Extension study.

• The most common adverse event in CLARITY and CLARITY Extension was lymphopenia, consistent with the mechanism of action of cladribine tablets.1-3

OBJECTIVES

• To evaluate the efficacy of cladribine tablets on B and T lymphocyte and natural killer (NK) cell profiles after the first administration of cladribine tablets in the ORACLE-MS, CLARITY and CLARITY Extension 4 studies.

METHODS

• A longitudinal (48 weeks) evaluation of peripheral blood lymphocyte subtypes was conducted for patients receiving the first course of cladribine tablets either as part of the initial 3.5 mg/kg active treatment groups (ORACLE-MS and CLARITY) or the placebo-switched-to-active-treatment group (CLARITY Extension).

• Patients from CLARITY Extension included in this analysis had received placebo in CLARITY and switched to cladribine tablets 3.5 mg/kg in the extension phase. For these patients, lymphocyte surface markers (LSM) measurements that were available in CLARITY are included in the CLARITY Placebo group.

• Lymphocyte subtype analyses were performed using flow cytometry to detect lymphocytes expressing CD3+, CD4+, CD8+, CD16+/56+ or CD19+.

• Blood samples for the LSM analysis were collected from a subset of patients in each study, and immunophenotypes are reported at baseline and at Week 0, 13, 24 and 48.

• Changes in absolute cell numbers and changes in the relative proportion of the lymphocyte subtypes were evaluated.

• Patients with at least one LSM assessment were included in this analysis.

• Patients who received rescue medication in CLARITY/CLARITY Extension, or interferon beta-1a in ORACLE-MS, had their LSM data censored from the time of the first rescue/interferon beta-1a administration.

RESULTS

Patients

• Baseline demographics and clinical characteristics of patients with LSM data from CLARITY, CLARITY Extension and ORACLE-MS are shown in Table 1.

• The baseline distributions of absolute lymphocyte counts (ALC) were similar across the 3 studies.

Table 1. Baseline Demographics and Clinical Characteristics of Patients Included in the LSM Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>Female (%)</th>
<th>On study to end of 1 year (%)</th>
<th>On study to end of 12 weeks (%)</th>
<th>On study to end of 24 weeks (%)</th>
<th>On study to end of 36 weeks (%)</th>
<th>On study to end of 48 weeks (%)</th>
<th>Pre-LM 53 VLA (closest)</th>
<th>Pre-LM 63 VLA (closest)</th>
<th>Pre-LM 108 (closest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLARITY Placebo</td>
<td>36 (16.6)</td>
<td>87 (67.2)</td>
<td>100 (75)</td>
<td>100 (75)</td>
<td>100 (75)</td>
<td>100 (75)</td>
<td>100 (75)</td>
<td>61 (71.6)</td>
<td>62 (72.7)</td>
<td>67 (74.1)</td>
</tr>
<tr>
<td>CLARITY CT 3.5</td>
<td>35 (16.5)</td>
<td>87 (68.4)</td>
<td>93 (68)</td>
<td>96 (70)</td>
<td>93 (68)</td>
<td>95 (70)</td>
<td>96 (70)</td>
<td>61 (71.6)</td>
<td>62 (72.7)</td>
<td>67 (74.1)</td>
</tr>
<tr>
<td>CLARITY Ext CT 3.5</td>
<td>35 (17.0)</td>
<td>87 (68.4)</td>
<td>93 (68)</td>
<td>96 (70)</td>
<td>93 (68)</td>
<td>95 (70)</td>
<td>96 (70)</td>
<td>61 (71.6)</td>
<td>62 (72.7)</td>
<td>67 (74.1)</td>
</tr>
<tr>
<td>ORACLE-MS CT 3.5</td>
<td>35 (16.4)</td>
<td>87 (67.1)</td>
<td>93 (68)</td>
<td>96 (70)</td>
<td>93 (68)</td>
<td>95 (70)</td>
<td>96 (70)</td>
<td>62 (72.7)</td>
<td>63 (77.4)</td>
<td>69 (77.1)</td>
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</tbody>
</table>

Lymphocyte Subtype Profiles

• Profiles of CD16+/CD56+ NK lymphocytes, CD19+ B lymphocytes, and CD4+ and CD8+ T lymphocytes were generally consistent across studies (Figure 1).

• CD16+/CD56+ NK cells were transiently reduced with cladribine tablets, with a prominent reduction at Week 5 followed by reconstitution towards baseline from Week 12 to 48. The interquartile ranges for lymphocyte subtypes and placebo patients overlapped for the majority of the observation period.

• A large reduction in cell numbers occurred in the CD19+ B cell compartment (reduction from baseline of approximately 73% at Week 13 in each study).

• Nadir was achieved at Week 13, followed by reconstitution towards baseline from Week 24 to 48.

• CD4+ and CD8+ T cells were also markedly reduced in numbers, but to a lesser degree than CD16+/CD56+ NK cells and CD19+ B cells.

• Reductions of both CD4+ and CD8+ T cells were discontinuous, but had not fully returned to baseline at Week 48 in patients treated with cladribine tablets in each study.

Lymphocyte Subtype Proportions of ALC

• The changes from baseline in CD16+/CD56+ NK cells and CD19+ B cells as proportions of ALC are shown in Figure 2.

• CD16+/CD56+ NK cell proportions increased by 5% to 15% at 13 weeks and by 28% to 38% at Week 48 compared with baseline lymphocyte subtype proportions.

Lymphocyte Subtype Proportions of CLARITY

• The changes from baseline in CD3+, CD4+ and CD8+ T cells as proportions of ALC are shown in Figure 3.

• CD3+, CD4+ and CD8+ T cell proportions of ALC decreased by 2% to 4% and by 2% to 10% at Week 48, compared with baseline lymphocyte subtype proportions in patients treated with cladribine tablets in CLARITY, CLARITY Extension or ORACLE-MS.

• The changes from baseline in CD3+, CD4+ and CD8+ T cells as proportions of ALC decreased by 2% to 4% and by 2% to 10% at Week 48, compared with baseline lymphocyte subtype proportions.

CONCLUSIONS

• Patients treated with cladribine tablets, early decreases in NK cells were observed followed by rapid recovery; there was a lagging delay of over 1 year in interquartile ranges between cladribine tablets and placebo.

• Peripheral B cell reductions were discontinuous, with an early reduction of counts followed by a rapid reconstitution towards baseline. This effect was consistent across the 3 studies.

• There was a moderate and discontinuous reduction in T cell counts, which was more pronounced in CD8+ than CD4+ T lymphocytes.

• Changes in B cells as a proportion of ALC at 13 weeks varied from 0% to 38% in all studies.

• At Week 48, there was a small reduction from baseline in CD4+ T cells as a proportion of the ALC.

REFERENCES


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