INTRODUCTION

- In CLARITY, treatment with Cladribine Tablets showed strong efficacy in patients with relapsing multiple sclerosis (RMS) versus placebo up to 2 years.1
- In CLARITY Extension, Cladribine Tablets produced durable clinical benefits: there was no difference in clinical efficacy between treatment with Cladribine Tablets in CLARITY followed by placebo in CLARITY Extension versus treatment with Cladribine Tablets in both CLARITY and CLARITY Extension.
- Patients with RMS and high disease activity (HDA) may be at higher risk of relapses and disability progression2.
- In a post hoc analysis of CLARITY, patients with HDA had clinical and magnetic resonance imaging responses to Cladribine Tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) that were generally better than, or comparable with, the overall population.3
- Lymphopenia is an anticipated side effect of cladribine treatment due to its pharmacological properties leading to selective depletion of lymphocytes, as observed in CLARITY and CLARITY Extension.1,2
- While there does not appear to be a direct link between lymphocyte count reduction and clinical or MRI outcomes, it is relevant to investigate whether HDA patients are more likely to experience lower lymphocyte counts.

OBJECTIVE

- To determine the rate of lymphopenia in patients with HDA in the CLARITY/CLARITY Extension studies in patients receiving Cladribine Tablets 3.5 mg/kg in CLARITY and either Cladribine Tablets 3.5 mg/kg or placebo in CLARITY Extension.

METHODS

- In this post hoc analysis, patients exposed to Cladribine Tablets 3.5 mg/kg in CLARITY or CLARITY Extension in Years 1 and 2 only are referred to as the CT 3.5 group (n = 685) and a subgroup of these patients who received further courses of Cladribine Tablets 3.5 mg/kg in Years 3 and 4 are referred to as the CT 7.0 group (n = 194) (see Figure 1 for study design).
- Lymphopenia in HDA and non-HDA subgroups was analysed based on the Expanded Access Event of Special Interest (AESI) lymphopenia (all Medical Dictionary for Regulatory Activities [MedDRA] preferred terms describing a drop in lymphocytes) and on laboratory data for absolute lymphocyte count (ALC) across CLARITY and CLARITY Ext.
- Two overlapping sets of criteria (Figure 2) were applied in the analysis of baseline disease characteristics to subdivide patients into HDA groups based upon:
  - High relapse activity (HRA), defined as 2 relapses in the year before study entry whether on disease modifying drug (DMD) treatment or not;
  - HRA + disease activity on treatment (DAT), defined as ≥ 1 relapse in the year before study entry while on therapy with other DMDs and ≥ 1 T1 gadolinium-enhancing or ≥ 9 T2 lesions.

RESULTS

Lymphopenia based on adverse event reporting

- In the CT 3.5 group, the incidence rates of AESI lymphopenia were similar for the two HDA subgroups and the corresponding HDA and non-HDA subgroups (Table 1).
- In CT 3.5 at Year 2, AESI≥100 patient-years were similar in the HRA (n = 190) and HRA+DAT (n = 219) subgroups (11.50 and 13.09 respectively) and similar between corresponding non-HDA groups (14.08 [n = 489] and 13.46 [n = 466]).
- In CT 7.0 at Year 2, but not different between HDA and non-HDA subgroups.
- There was a low rate of serious AESI lymphopenia in the CT 3.5 HRA and non-HRA groups and no incidences in the CT 7.5 HRA and non-HRA groups (Table 1).
- A similar pattern was seen in the CT 7.0 group at Year 4, but with lower nadirs and for CT 3.5 at Year 2. However, it should be noted that this difference is not profound and that patient numbers in the CT 7.0 group were lower than in the CT 3.5 group.
- There were only small differences in time to ALC nadir between HDA subgroups (Table 3).

Figure 2. Definitions of High Disease Activity

Table 1. AESI Lymphopenia for HDA and Corresponding Non-HDA Subgroups Over 2 yearsa

<table>
<thead>
<tr>
<th>Year</th>
<th>HRA</th>
<th>Non-HRA</th>
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<tbody>
<tr>
<td>1</td>
<td>1.86</td>
<td>2.40</td>
</tr>
<tr>
<td>2</td>
<td>1.86</td>
<td>2.40</td>
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aAESI≥100 patient-years were similar in the HRA (n = 190) and HRA+DAT (n = 219) subgroups (11.50 and 13.09 respectively) and similar between corresponding non-HDA groups (14.08 [n = 489] and 13.46 [n = 466]).

DISCLOSURES

BC has received honoraria for lectures/consultations from Merck, Bayer Healthcare, Sanofi-Aventis, Neurology Reviews, Biogen Idec, Teva Pharmaceuticals, and Acticore. Biomed, Inc. has served as an advisory board for Bayer Healthcare, Merck, Acrisolve, Biomed, Teva Pharmaceuticals, and Biogen. G. Giovannoni has received grant support from Biogen Idec and consulting honoraria from Biogen Idec, Merck, Bayer, Biogen Idec and Teva, and has received speaker honoraria from Biogen Idec, Merck, Novartis, Merck KGaA, and Sanofi-Aventis. T. Patients have received speaker honoraria from Biogen Idec, Merck, Novartis, and Ironwood. J. J. Hall has received speaker honoraria and consulting fees from Biogen Idec, Merck, Sanofi-Aventis, Teva, and Novartis, and has served as advisory board member for Biogen Idec, Merck, and Novartis. J. C. P. Soelberg has served as an advisory board member for Biogen Idec, Merck, Teva, and Novartis, and has received consulting fees from Biogen Idec, Merck, and Novartis. C. M. Barrington has served as an advisory board member for Biogen Idec, Merck, and Novartis. A. C. G. Hill has received honoraria for lectures/consultations from Merck, Biogen, and SD Biosciences. N. A. The study was sponsored by Biogen Idec, Inc., a business of Merck KGaA, Darmstadt, Germany (in the USA) and Merck Serono SA – Geneva, an affiliate of Merck KGaA, Darmstadt, Germany. The authors would like to thank their patients and the investigators, co-investigators, and the study teams at each of the participating centers for the CLARITY/CLARITY Extension trials and the study teams at each of the participating centers for the CLARITY/CLARITY Extension trials. Medical writing assistance was provided by Peter J. P. Cheek of CStone Communications, Spring Gardens, Chester, UK, and was funded by Merck KGaA, Darmstadt, Germany.

REFERENCES


CONCLUSIONS

- There were no relevant differences between the HDA and non-HDA subgroups with regard to incidence of the AESI lymphopenia, ALC nadir, and time to ALC nadir.
- There were no relevant differences between the HRA and HRA+DAT subgroups with regard to incidence of the AESI lymphopenia and ALC nadir, suggesting the inclusion of previously treated patients did not change the risk and the severity of lymphopenia.
- It should be noted, however, that DAT patients represented only a small proportion of additional HDA patients.
- Patients who received CT 3.5 mg/kg had a lower incidence of AESI lymphopenia than patients who received CT 7.0 mg/kg.