INTRODUCTION

• CLARITY was a large (1326 patients), randomized, double-blind study in patients with early and moderately advanced relapsing-remitting multiple sclerosis (RRMS) (see Figure 1 for study design), in which treatment with cladribine tablets showed strong efficacy versus placebo (PBO) over 2 years.1

• Patients with RMS who show an increased rate of relapse or disability progression are at high risk for irreversible disability. Analysis of CLARITY may provide insights into the efficacy of cladribine tablets in patients with evidence of HDA.

OBJECTIVE

• To compare the effects of cladribine tablets 3.5 mg/kg versus placebo on outcomes assessed by magnetic resonance imaging (MRI) in subgroups of CLARITY patients with evidence of HDA at study entry, using two HDA definitions.

METHODS

• The CLARITY study enrolled patients aged 18–50 years with a definite diagnosis of relapsing-remitting multiple sclerosis (RRMS):
  – 1 relapse in the 12 months before study entry, but no relapses within the 26 days before study entry; or
  – neurological lesions detectable by MRI consistent with MS.

• Clinicians were asked if they had received a disease-modifying drug (DMD) within 3 months before study entry or treatment with ≥ 1 DMD had failed.

• CLARITY randomized patients to cladribine tablets 3.5 mg/kg (n = 435) or placebo (n = 430) = 865 patients = 419 patients randomized to placebo (n = 210) or cladribine tablets

• Two overlapping sets of criteria (Figure 2) were applied in the analysis of cumulative disease characteristics to subdivide patients into HDA groups based upon:
  1. High relapse activity (HRA): patients with ≥ 2 relapses in the year before study entry, regardless of prior use of DMD.
  2. Treatment nonresponse (TNR): patients with ≥ 2 relapses in the year before study entry, regardless of prior use of DMD, plus patients with 1 relapse AND ≥ 1 gadolinium-enhancing (Gd+) or ≥ 9 T2 lesions in the year before study entry, while on DMD therapy. Treatment with cladribine tablets 3.5 mg/kg over 2 years. Placebo

RESULTS

• Patients

• Demographics and disease characteristics were similar across the subgroups of patients who met the HDA definitions (Table 1). The demographic and disease characteristics of patients who did not meet the HDA criteria were also similar across the subgroups (data not shown).

• The overall analysis involved 870 patients randomized to placebo (n = 430) or cladribine tablets 3.5 mg/kg (n = 437).

• In those who did not meet the HRA+TNR criteria (i.e. non-HRA+TNR patients), 286 placed in placebo and 203 received cladribine tablets 3.5 mg/kg.

• The overall analysis involved 870 patients randomized to placebo (n = 430) or cladribine tablets 3.5 mg/kg (n = 437). The demographics and disease characteristics of patients who did not fulfill the HDA criteria were also similar across the subgroups (data not shown).

• Efficacy analyses from CLARITY assessed the overall population and HDA subgroups and corresponded non-HDA subgroups based on cumulative numbers of new T1 Gd+ lesions, cumulative numbers of T2 lesions, and cumulative numbers of new or enlarging combination (CU) lesions (defined as a new T1 Gd+ lesion, or a new or enlarging T2 lesion, on both, without double-counting).

• All HDA analyses were post hoc and not pre-specified; no multiplicity adjustments were done in the resulting P values. All comparisons where the P value was less than 0.05 by statistical testing should be regarded as nominally significant.

Figure 1. CLARITY Study Design

Figure 2. Definitions of High Disease Activity

Table 1. Patient Demographics and Disease Characteristics by HDA Subgroup

Figure 3. Forest Plot of Relative Risk of Active T2 Lesions by HDA Subgroup for Cladribine Tablets 3.5 mg/kg versus Placebo

Table 2. Summary of Cumulative MRI Outcomes with Cladribine Tablets in High Disease Activity Subgroups of Patients with Relapsing-Romotting MS

Figure 4. Forest Plot of Relative Risk of Combined New Lesions by HDA Subgroup for Cladribine Tablets 3.5 mg/kg versus Placebo

CONCLUSIONS

• Patients with RMS in the CLARITY study, treatment with cladribine tablets 3.5 mg/kg produced statistically significant effects versus placebo on cumulative new T1 Gd+ lesions, active T2 lesions, and cumulative CU lesions in two subgroups of patients selected using HDA criteria.

• In both HDA subgroups, there was a consistent treatment effect on radiological outcomes with cladribine tablets 3.5 mg/kg irrespective of disease activity before entry to the CLARITY study, or prior DMD use.

REFERENCES


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DISCLOSURES

• GG has received speaker honoraria and consulting fees from Abbvie, Alba Bio, Amnial, Bayer Schering Pharma, Biogen Idec, Canaffissel, Gliopause, Genentech, Merck, Pfizer, Inc., Pﬁzer-Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi Genzyme, UCB, and writing assistance from Chester, UK, and was funded by Merck KGaA, Darmstadt, Germany (ROW). The authors would like to thank patients and their families, investigators, co-investigators, and site personnel at all participating sites for making the CLARITY study possible. The authors would like to thank patients and their families, investigators, co-investigators, and site personnel at all participating sites for making the CLARITY study possible.