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Alemtuzumab improves neurological functional systems in treatment-naive relapsing-remitting multiple sclerosis patients

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ABSTRACT

Background: Individual functional system scores (FSS) of the Expanded Disability Status Scale (EDSS) play a central role in determining the overall EDSS score in patients with early-stage multiple sclerosis (MS). Alemtuzumab treatment improves preexisting disability for many patients; however, it is unknown whether improvement is specific to certain functional systems.
Objective: We assessed the effect of alemtuzumab on individual FSS of the EDSS.
Methods: CAMMS223 was a 36-month, rater-blinded, phase 2 trial; treatment-naive patients with active relapsing-remitting MS, EDSS ≤3, and symptom onset within 3 years were randomized to annual courses of alemtuzumab or subcutaneous interferon beta-1a (SC IFNB-1a) 44 μg three times weekly.
Results: Alemtuzumab-treated patients had improved outcomes versus SC IFNB-1a patients on most FSS at Month 36; the greatest effect occurred for sensory, pyramidal, and cerebellar FSS. Among patients who experienced 6-month sustained accumulation of disability, clinical worsening occurred most frequently in the brainstem and sensory systems. For patients with 6-month sustained reduction in preexisting disability, pyramidal and sensory systems contributed most frequently to clinical improvement.
Conclusions: Alemtuzumab demonstrated a broad treatment effect in improving preexisting disability. These findings may influence treatment decisions in patients with early, active relapsing-remitting MS displaying neurological deficits. ClinicalTrials.gov Identifier NCT00050778.

1. Introduction

Alemtuzumab (LEMTRADA™) is a humanized monoclonal antibody that selectively targets CD52 to deplete circulating T and B lymphocytes, thought to be critical mediators of multiple sclerosis (MS) inflammatory processes [1,2]. After lymphocyte depletion, a distinctive pattern of T- and B-cell repopulation begins within weeks, leading to a rebalanced immune system [3,4]. Alemtuzumab is approved in many countries as treatment for adult patients with relapsing-remitting MS (RRMS) who also meet country-specific selection criteria. Alemtuzumab has been evaluated in one 3-year phase 2 trial (CAMMS223, ClinicalTrials.gov identifier NCT00050778) [5] and two 2-year phase 3 studies (Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis I [CARE-MS I, NCT00530348] and CARE-MS II [NCT00548405]) [6,7]. Alemtuzumab significantly reduced the risk of relapse and showed significant benefit on many radiological outcomes versus subcutaneous interferon beta-1a (SC IFNB-1a, Rebif®; EMD Serono, Inc., Rockland, MA) in active RRMS patients who were treatment-naive (CAMMS233 and CARE-MS I) [5,6] or who had inadequate efficacy response, defined as at least one relapse, to prior therapy (CARE-MS II) [7]. Safety findings with alemtuzumab were consistent across trials, with the most common adverse events being infusion-associated reactions; other notable adverse events were infections and autoimmune adverse events [5–8].

Disability in patients with MS is commonly assessed using the Expanded Disability Status Scale (EDSS), which is a 10-point scale with 0.5-point steps based on seven functional systems [9]. These functional systems measure different aspects of disability, i.e., impairments in bowel/bladder, brainstem, cerebellar, cerebral, pyramidal, sensory, and visual functioning. In the early stages of MS, individual functional systems of the EDSS play a greater role than ambulatory impairment in determining the overall EDSS score, and patients are more likely to experience deficits in the functional systems of pyramidal, cerebellar, brainstem, and sensory than in the systems of visual, bowel/bladder, and cerebral [10].

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At enrollment, patients in CAMMS223 had low levels of physical disability (defined as EDSS score ≤ 3), as is the case with many MS patients in clinical trials [11–14]. In this trial, the rate of sustained accumulation of disability (SAD; defined as an increase from baseline in EDSS score of ≥1.0 [≥1.5 in patients with a baseline EDSS score of 0]) confirmed over 6 months was reduced by 71% with alemtuzumab versus SC IFNB-1a ($p < 0.001$). Disability measured by mean EDSS score over time also decreased significantly with alemtuzumab, but increased with SC IFNB-1a. Furthermore, sustained reduction in preexisting disability (SRD; a decrease from baseline by ≥1 EDSS point in patients with baseline EDSS scores ≥ 2.0) confirmed over 6 months was significantly more likely to be observed in alemtuzumab patients [8]. More recently, similar results for these disability endpoints were reported for patients enrolled in CARE-MS II [7].

In the present analysis of CAMMS223, we examined the treatment effect of alemtuzumab compared with SC IFNB-1a on each of the individual EDSS functional systems to determine if alemtuzumab's beneficial treatment effect is broadly based or specific to certain functional systems. Additionally, we examined the relationship between overall EDSS and the functional systems to understand which systems contribute to SAD and to SRD among alemtuzumab-treated patients.

2. Methods

Detailed methods for CAMMS223 have previously been published [5]; a brief summary is provided here.

2.1. Patients

Treatment-naive patients with RRMS with EDSS scores of ≤3.0, MS symptom onset within 3 years, at least two relapses in the previous 2 years, and evidence of at least one gadolinium-enhancing lesion on any of up to four monthly screening MRI scans were randomized to the study. Due to a misdiagnosis of MS, one patient was not included in the efficacy analyses. Ethics board approvals were obtained from all sites, and all patients provided written informed consent.

2.2. Study design

CAMMS223 was a 3-year, rater-blinded, active-controlled, head-to-head, phase 2 trial. Patients were randomly allocated in a 1:1 ratio to receive alemtuzumab 12 mg or SC IFNB-1a (44 μg three times per week). Other patients were randomized to receive alemtuzumab 24 mg. However, since the 24-mg dose level is not approved for use in treatment of MS in any jurisdiction and is no longer being studied, and given the robust effects observed at the 12-mg dose, analyses of the 24-mg group are omitted from this report. Alemtuzumab was administered via intravenous infusions on 5 consecutive days at baseline and on 3 consecutive days 12 months and 24 months later (the latter course was optional and at the discretion of the treating physician if the $CD4^+$ T-cell count was $\geq 100 \times 10^6$ cells/L). In September 2005, alemtuzumab dosing within the trial was suspended after immune thrombocytopenia developed in three patients (including the fatal index case). All safety and efficacy assessments proceeded as planned, and patients in the SC IFNB-1a group continued to receive medication [5]. The alemtuzumab dosing suspension was lifted in April 2008 [15]. As a result of the suspension, 75% of patients were precluded from receiving the optional third course of alemtuzumab at Month 24.

2.3. Study outcomes

The results of this study represent Class I evidence due to several characteristics of the study design. Those assessments in the study pertaining to the key efficacy endpoints (e.g., EDSS for disability and relapse) used masked raters. The study was randomized to ensure that the baseline characteristics were comparable between treatment arms.

2.4. Disability assessment

The EDSS score was assessed at baseline and quarterly using the "Neurostatus" training and scoring system [16] by a neurologist blinded to treatment arms. The functional systems assessed in the present analysis were bowel/bladder, brainstem, cerebellar, cerebral, pyramidal, sensory, and visual.

2.5. Statistical analysis

Summary statistics of observed values and change from baseline were calculated for each functional system at each time point. For functional system scores (FSS) that included a letter for subclass identification (such as 1X, 2A, and 3B), only the numeric portion was used for the statistical analysis. A significance level of 0.05 was used for these post hoc analyses, and no adjustment was made for multiple hypothesis testing. All FSS were evaluated equally throughout this analysis. All statistical tests were two-sided. Change from baseline for each functional system was categorized as improved (decreased FSS of at least 1.0 point), no change (stable FSS ±0.5 point), or worsened (increased FSS of at least 1.0 point). The overall treatment effect across all time points through Month 36 was tested with a repeated measures proportional odds model. The above analysis was also conducted using a subset of patients who had received only two annual courses of alemtuzumab.

Kaplan-Meier and Cox proportional hazards model analyses for each functional system were conducted for time to sustained (≥6 months) clinical worsening of functional system and time to sustained clinical improvement of functional system. Clinical worsening was defined as an on-treatment FSS increase of ≥2.0 points for patients with a baseline score ≤ 1.0, or any increase in score from a baseline FSS of ≥2.0 points. Clinical improvement was defined as a ≥1.0-point decrease in FSS for the subset of patients with baseline FSS ≥1.0. Analyses of visual and bowel/bladder functional systems used actual, not converted scores. Spearman correlation coefficients were used to compare FSS changes from baseline at Months 6 and 36. For patients with 6-month SAD in EDSS, the number of patients with worsening in each functional system at the time of SAD was counted. For patients with 6-month SRD in EDSS, the number of patients with improvement in each functional system at the time of SRD was counted.

3. Results

3.1. Patients

Complete demographic and baseline clinical characteristics and patient disposition have been previously reported [5]. Baseline characteristics were well-balanced between the SC IFNB-1a ($N = 111$) and alemtuzumab 12-mg ($N = 112$) treatment groups. The mean age of the total population was 32.3 years, 64.3% were female, and 90.1% were Caucasian. The mean EDSS score was 1.9, 94.9% of patients had an EDSS score ≥ 1, and the mean time since first relapse was 1.5 years. Of the patients randomized to receive alemtuzumab 12 mg, 6 patients received only one course, 78 received two courses, and 24 received three courses during the core 36-month study.

3.2. Functional systems

All FSS were balanced between treatment groups at baseline. Within the alemtuzumab treatment group, the largest mean reductions from baseline to Month 36 occurred in the sensory (−0.28 points), pyramidal (−0.17 points), and cerebellar FSS (−0.15 points). Compared with patients receiving SC IFNB-1a, patients in the alemtuzumab group