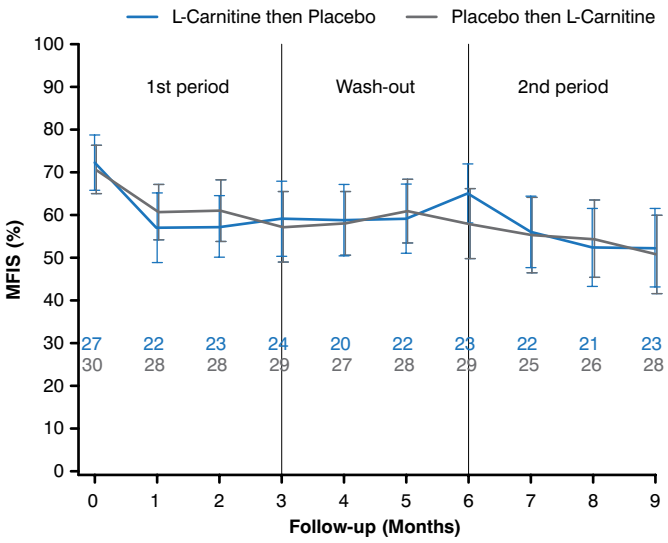
Figure 1. Effects of L-carnitine vs Placebo on Mean MFIS Score



MFIS, Modified Fatigue Impact Scale.
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The primary outcome measure was the 21-item MFIS global score. Secondary outcome measures included the Fatigue Severity Scale (FSS), Fatigue Visual Analog Scale (VAS), physical dimension scale of MFIS, and SEP-59 Quality of Life scale. Free carnitine and acyl-carnitine serum dosages were scheduled at baseline and at the end of the study. Carnitine levels at baseline were included in the model and were tested for correlations with fatigue. Mixed linear regression models were used to assess the effect of the treatment and the treatment-period interaction. Baseline carnitine levels were included in the model and were tested for correlations with fatigue.

Of the 59 randomized patients, 57 were included in the intention-to-treat analysis. The mean patient age was 45 years; 74% of the patients were women; and the median EDSS score was 3. The baseline mean MFIS score was 71.3%, and the mean FSS score was 6.1. No significant unexpected adverse events were reported throughout the study.

For the primary outcome, there was no significant difference in the mean MFIS score between the 2 treatment groups (–0.22 points; 95% CI, –5.80 to 5.36; $P = .94$; Figure 1). No significant difference was observed between the groups in the FSS score (–0.10 points; 95% CI, –0.45 to 0.24; $P = .55$).

For the VAS score, there was a significant difference between the groups in favor of placebo (1.43 points; 95% CI, 0.22 to 2.65; $P = .02$). Mild carnitine deficiency was detected in 7 patients at baseline. A more severe carnitine deficiency was found in 1 patient receiving treatment with cyclophosphamide, who received only placebo and dropped out after the washout period. L-carnitine was not effective for treating fatigue in the carnitine-deficient patients ($P = .24$). No evidence of efficacy was observed for the physical dimension of the MFIS, the SEP-59, the EDSS, walking ability, and other measures.

The results of this study showed that oral L-carnitine was not an effective treatment for MS fatigue when compared with placebo, even in patients with mild carnitine deficiency.

CARE-MS II Follow-up: Improvements With Alemtuzumab Maintained for 4 Years

Written by Emma Hitt Nichols, PhD

Improvements in annualized relapse rate (ARR) and Expanded Disability Status Scale (EDSS) score were maintained throughout 4 years following treatment with alemtuzumab for 2 years in patients with relapsing-remitting multiple sclerosis (RRMS) who relapsed on prior therapy. Hans-Peter Hartung, MD, Heinrich Heine University, Düsseldorf, Germany, presented data from the Extension Protocol for Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab trial [NCT00930553; Hartung H-P et al. ECTRIMS 2014 (poster P043)].

A humanized anti-CD52 monoclonal antibody, alemtuzumab is approved for the treatment of specific forms of relapsing MS in multiple countries. In the CARE-MS II trial, the ARR was reduced by 49% compared with subcutaneous interferon beta-1a (SC IFN-β-1a) at 2 years in patients with RRMS who relapsed on prior therapy [Coles AJ et al. *Lancet* 2012]. In addition, the reduction in relapses and improvement in MRI outcomes were maintained through year 3 during the open-label CARE-MS II extension trial, with around 80% of patients not requiring retreatment or treatment with another therapy [Fox EJ et al. AAN 2013 (S41.001)]. The purpose of this analysis was to evaluate the efficacy and safety of alemtuzumab through year 4 in patients who received alemtuzumab in the core study and those who switched to alemtuzumab in the extension trial.

In the phase 3 CARE-MS II trial, patients with RRMS were randomly assigned to receive 2 annual courses of

alemtuzumab or SC IFN-β-1a 3 times per week for 2 years [Coles AJ et al. *Lancet* 2012]. Patients who completed CARE-MS II were eligible to enroll in the extension study, in which patients who had received alemtuzumab in the core trial received alemtuzumab retreatment as needed and patients who switched from SC IFN-β-1a received alemtuzumab at the beginning of the extension period and 12 months later, then retreatment as needed [Fox EJ et al. AAN 2013 (S41.001)].

Of the 393 patients from the alemtuzumab arm in CARE-MS II who enrolled in the extension trial, 68% did not require retreatment with alemtuzumab and only 5% required treatment with another disease-modifying therapy (DMT). The reduction in ARR achieved during CARE-MS II at years 0 to 2 (0.26 with alemtuzumab vs 0.52 with SC IFN-β-1a) was maintained through year 4 with a rate of 0.23. In addition, the change in EDSS from baseline was maintained or improved in 69.2% of patients at year 4.

In patients who switched from SC IFN-β-1a to alemtuzumab, the ARR was decreased by 71% (from 0.52 to 0.15) during the first 2 years of alemtuzumab treatment .

The majority of adverse events (AEs) were mild to moderate and were similar to those observed in the core trial, with common AEs including nasopharyngitis, urinary tract infection, and upper respiratory tract infection throughout 4 years. Thyroid AEs occurred with a cumulative incidence of 34.7% during the 4 years, which peaked in year 3 and decreased in year 4. Discontinuation of alemtuzumab due to treatment-related AEs occurred in 4.1% of patients who received alemtuzumab in the core trial and 4.2% in patients who received SC IFN-β-1a in the core trial.

In conclusion, Prof Hartung indicated that the data from this analysis show that improvements in ARR and EDSS achieved with alemtuzumab treatment for 2 years were maintained throughout 4 years, with a minority of patients requiring retreatment. In addition, there were no unexpected AEs.

CARE-MS I Follow-up: Alemtuzumab Efficacy, Safety for MS Treatment Maintained for More Than 4 Years

Written by Brian Hoyle

An Extension Protocol for Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab [NCT00930553; Coles AJ et al. ECTRIMS 2014 (poster P090)], a follow-up to the phase 3, randomized, head-to-head CARE-MS I study [NCT00530348], has demonstrated the continuing efficacy and safety of subcutaneous alemtuzumab in treatment-naïve patients with relapsing-remitting multiple sclerosis (RRMS) who were treated for up to 4 years. The findings of the multinational team of researchers were presented by Alasdair J. Coles, MD, University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom.

Alemtuzumab is a monoclonal antibody that targets CD52 and has received multinational approval as a treatment for relapsing MS. CARE-MS I documented the efficacy of alemtuzumab in significantly reducing the 2-year relapse rate compared with subcutaneous interferon beta-1a (SC IFN-β-1a) [Cohen JA et al. *Lancet*. 2012]. There were similar findings in the open-label extension phase of the study at year 3. The present data were obtained at year 4.

Patients aged 18 to 50 years with active RRMS and a baseline Expanded Disability Status Scale (EDSS) score ≤3.0 had been randomized to SC IFN-β-1a or alemtuzumab. The core study lasted 24 months, followed by the open-label extension phase.

The open-label, as-needed treatment phase involved 349 patients (95%) who had been randomized to the alemtuzumab arm of the core study, and 144 patients (83%) who had received SC IFN-β-1a. Only 21% of the patients in the first group received an additional course of therapy, and only 5% received 2 courses; the remaining patients received treatment only during the 2-year core phase. Of the second group, 139 switched to alemtuzumab in the open-label phase. The baseline characteristics of all patients were similar concerning age, sex, race (white), EDSS score, time since the first episode of MS, and number of relapses in the year prior to study enrollment.

The annualized relapse rates for those receiving alemtuzumab in year 3 (0.19) and year 4 (0.14) were similar (0.18) to that in the 2-year core phase; during the 4 years, the annualized relapse rate was 0.16 (95% CI, 0.13 to 0.19). The relapse rate in patients receiving interferon was 0.39 in the core phase; after switching to alemtuzumab, the open-label phase relapse rate was 0.12. Disability as assessed using the EDSS was stable or improved from baseline in 79.3% of patients from year 3 to year 4 of the core phase, and the improvement in EDSS from year 0 to year 4 was 73.5%.

Concerning safety, the incidence of most adverse events, including infections (most commonly, nasopharyngitis, urinary tract infection, and upper respiratory tract infection), was similar during the core and open-label phases. Most adverse events were mild or moderate