## BRAVO Analysis: Laquinimod Reduces Brain Atrophy in Patients With RRMS

Written by Toni Rizzo

Laquinimod, an oral immunomodulator under development for the treatment of multiple sclerosis (MS), reduced whole brain atrophy in the ALLEGRO and BRAVO trials [Vollmer T et al. *Neurology.* 2012]. In the ALLEGRO trial, laquinimod reduced the median percent volume change (PVC) in gray and white matter [Filippi M et al. *J Neurol Neurosurg Psychiatry.* 2014]. This study, presented by Kunio Nakamura, PhD, McGill University, Montreal, Canada, analyzed the effect of laquinimod on the PVC in gray and white matter in the phase 3 BRAVO trial [Vollmer T et al. *J Neurol.* 2014], using a newly developed, longitudinal image analysis technique.

In the BRAVO trial, 1331 patients with relapsing-remitting MS (RRMS) were randomized to oral laquinimod (n = 434), oral placebo (n = 450), or intramuscular interferon beta-1a (IFN-β-1a) (n = 447) for 24 months. The PVC from baseline in gray and white matter was measured at years 1 and 2 using pairwise Jacobian integration (PJI) [Nakamura K et al. *Neuroimage Clin.* 2013]. The subgroup analysis of PVC was based on baseline gadolinium-enhancing (Gd+) lesion counts and the PVC in gray and white matter.

Baseline characteristics were similar among the groups, except for the T2 lesion volume and the percentage of patients with Gd+ lesions, both of which were lower in the placebo group. Baseline normalized gray and white matter volumes were comparable among the groups.

The mean PVC in gray matter from baseline to year 1 was –0.609 with placebo, –0.797 with IFN-β-1a (–31% reduction vs placebo; $P = .004$), and –0.338 with laquinimod (51% reduction vs placebo; $P < .001$). The mean PVC in gray matter from baseline to year 2 was –1.199 with placebo, –1.348 with IFN-β-1a (–12% reduction vs placebo; $P = .065$), and –0.862 with laquinimod (28% reduction vs placebo; $P < .001$). The mean PVC in gray matter from year 1 to year 2 was –0.606 with placebo, –0.563 with IFN-β-1a (7% reduction vs placebo; $P = .391$), and –0.574 with laquinimod (5% reduction vs placebo; $P = .422$).

The mean PVC in white matter from baseline to year 1 was –0.453 with placebo, –0.541 with IFN-b-1a (–20% reduction vs placebo; $P = .497$), and –0.274 with laquinimod (40% reduction vs placebo; $P = .001$). The mean PVC in white matter from baseline to year 2 was –0.801 with placebo, –0.978 with IFN-b-1a (–22% reduction vs placebo; $P = .180$), and –0.665 with laquinimod (17% reduction vs placebo; $P = .011$). The mean PVC in white matter from year 1 to year 2 was –0.363 with placebo, –0.451 with IFN-b-1a (24% reduction vs placebo; $P = .298$), and –0.402 with laquinimod (–11% reduction vs placebo; $P = .949$).

Patients with baseline GD+ lesions had greater decreases in gray and white matter volumes. The treatment effect of laquinimod was consistent within Gd-based subgroups.

In this analysis, laquinimod reduced the percent volume decrease in gray and white matter from baseline to year 2 compared with placebo. The overall results were consistent with those in the ALLEGRO trial [Filippi M et al. *J Neurol Neurosurg Psychiatry.* 2014]. The PJI method was sensitive for detecting treatment effects.

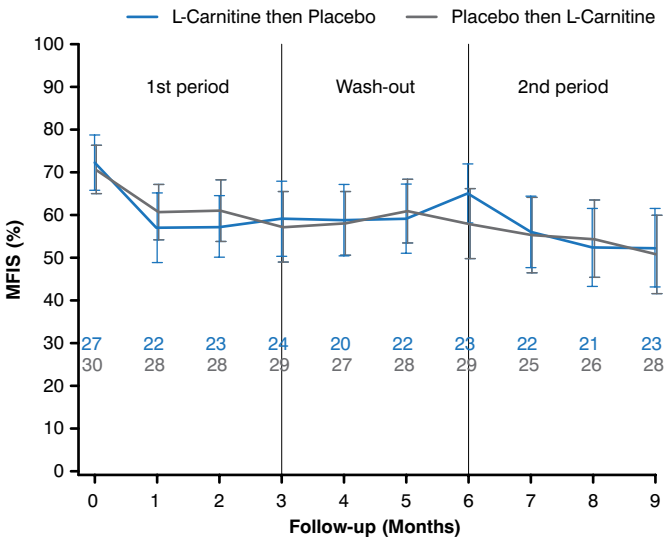
## FACTSEP Results: L-carnitine Not Effective for Treatment of Fatigue in MS Patients

Written by Toni Rizzo

Patients with multiple sclerosis (MS) commonly suffer from fatigue that negatively affects their functioning and quality of life. Both the cause and the consequences of MS fatigue are multidimensional and require multidisciplinary treatment for successful symptom management. The fatigue is thought to be associated with low blood carnitine levels, and some evidence suggests that carnitine might improve symptoms [Tejani AM et al. *Cochrane Database Syst Rev.* 2012]. The results of the Efficacy of L-carnitine Versus Placebo in the Treatment of Fatigue in Multiple Sclerosis study [FACTSEP; NCT01149525] were presented by Jean-Christophe Ouallet, MD, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France.

This multicenter double-blind crossover study enrolled 59 patients with relapsing-remitting MS, secondary-progressive MS, or primary-progressive MS with an Expanded Disability Status Scale (EDSS) score ≤ 6.0 and fatigue lasting > 3 months, with a global Modified Fatigue Impact Scale (MFIS) score > 45%. The patients were randomized to treatment with L-carnitine (2 g, oral solution, twice a day; n = 29) versus placebo (n = 30) for 3 months. After 3 months, all patients underwent a 3-month washout period, after which the initial L-carnitine group switched to placebo and the initial placebo group switched to L-carnitine for 3 months.

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




MFIS, Modified Fatigue Impact Scale.
Reproduced with permission from JC Ouallet, MD.

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