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

in severity. Only 5 of 376 patients (1.3%) withdrew due to adverse events.

The efficacy of alemtuzumab in treatment of RRMS in patients who were treatment-naïve at baseline, which was noted at 2 and 3 years, was maintained at 4 years. Safety was also similar in patients who received alemtuzumab throughout the study and those who switched from interferon after the first 2 years. No new or unexpected adverse events appeared during year 4. The present data further bolster the acceptability of alemtuzumab treatment for this population of patients with MS.

RPC1063 Safe and Effective in RRMS

Written by Emma Hitt Nichols, PhD

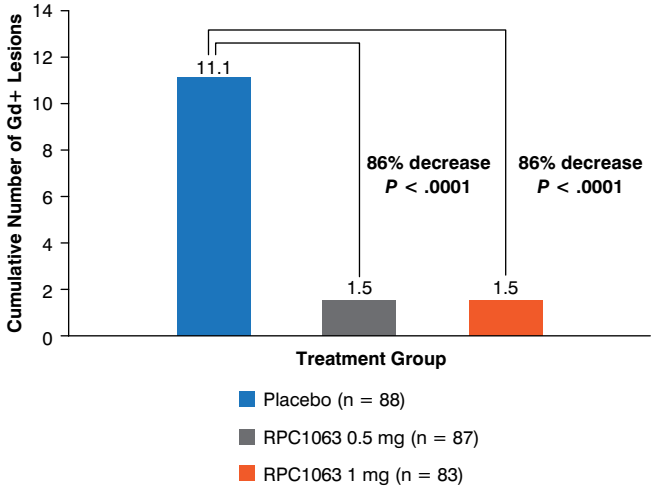
Treatment with the sphingosine 1-phosphate (S1P) receptor modulator, RPC1063, resulted in a substantial decrease in gadolinium-enhancing (Gd+) lesions and the number of new or enlarging T2 lesions in patients with relapsing-remitting multiple sclerosis (RRMS). Amit Bar-Or, MD, Montreal Neurological Institute, Montreal, Ontario, Canada, presented data from the Efficacy and Safety Study of RPC1063 in Relapsing Multiple Sclerosis Patients trial [Radiance Study; NCT01628393].

Targeting the S1P receptor family is an approach that has been explored as a treatment for patients with RRMS [Halmer R, Walter S, Fasbender K. *Cell Physiol Biochem*. 2014. RPC1063 is a novel agent that modulates S1P receptors 1 and 5, and has been previously evaluated in healthy subjects. The purpose of the Radiance Study was to further evaluate RPC1063 in patients with RRMS.

In the phase 2 Radiance Study, 258 adult patients with RRMS were randomly assigned to receive 24 weeks of 0.5 mg or 1 mg of RPC1063, or placebo. Upon completion of the treatment period, a blinded extension study was conducted in which patients who received RPC1063 continued treatment, and patients who received placebo were assigned to 0.5 mg or 1 mg of RPC1063. Patients aged 18 to 55 were eligible to enroll in the study if they had an Expanded Disability Status Scale (EDSS) score of 0 to 5.0 at baseline and met ≥1 of the RRMS criteria, which included ≥1 documented relapse within the prior 12 months, or ≥1 documented relapse plus ≥1 Gd+ lesion(s) within the previous 24 months.

The primary end point of the Radiance Study was the cumulative number of Gd+ lesions. Secondary end points included the number of Gd+ lesions at week 24, the number of cumulative or enlarging T2 lesions, and the annualized relapse rate (ARR). At baseline, the mean EDSS score ranged from 2.85 to 2.94, the mean number of relapses over 12 months from 1.3 to 1.5, and the number of Gd+ lesions from 0.9 to 1.4.

Figure 1. Effect of RPC1063 on Total Number of Gd+ Lesions Over 12 Weeks



Gd+, gadolinium-enhancing.

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The cumulative number of Gd+ lesions significantly decreased by 86% ($P<.0001$) in patients who received either dose of RPC1063 as compared with patients who received the placebo from week 12 to 24 (Figure 1). In addition, at week 24, the mean number of Gd+ lesions significantly decreased by 91% and 94% ($P<.0001$ for both) in patients who received 0.5 mg and 1 mg of RPC1063, respectively, as compared with patients who received the placebo. Similarly, the cumulative number of new or enlarging T2 lesions significantly decreased by 84% and 91% ($P<.0001$ for both) in the 0.5 mg and 1 mg RPC1063 arms as compared with the placebo arm from week 12 to week 24. There was a dose-dependent trend toward a decrease in ARR, with a rate of 0.5 in the placebo arm, 0.35 in the 0.5-mg RPC1063 arm, and 0.24 in the 1-mg RPC1063 arm.

During the core, 24-week portion of the Radiance Study, the number of patients who experienced ≥1 treatment-emergent adverse event (TEAE) was 59.1% in the placebo arm, and 56% and 47% in the 0.5-mg and 1-mg RPC1063 arms, respectively. The most common TEAEs in patients who received RPC1063 included nasopharyngitis, headache, and urinary tract infection. During the study, 3 serious TEAEs were reported but deemed unrelated to the study drug. However, there were 3 cases of elevated alanine aminotransferase (≥3