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DURABLE EFFECTS OF ALEMTUZUMAB ON RELAPSE RATE OVER TIME IN CARE-MS II

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INTRODUCTION

- Alemtuzumab is a humanized monoclonal antibody that selectively targets CD52 to deplete circulating T and B lymphocytes; lymphocyte depletion is followed by a distinctive pattern of T- and B-cell repopulation[1,2]
- In the phase 3 Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis (CARE-MS) studies,[3,4] alemtuzumab 12 mg given annually showed superior efficacy over 2 years compared with subcutaneous interferon beta-1a (SC IFNB-1a, Rebif®) 44 µg given 3 times per week in patients with relapsing-remitting MS (RRMS)
  - In CARE-MS I, which enrolled treatment-naïve patients, alemtuzumab reduced the relapse rate by 55% (p<0.0001); there was a nonsignificant 30% reduction in sustained accumulation of disability (SAD) (alemtuzumab, 8% vs. SC IFNB-1a, 11%; p=0.22)[3]
  - In CARE-MS II, which enrolled patients with disease activity despite disease-modifying therapy, alemtuzumab reduced the relapse rate by 49% (p<0.0001) and risk of SAD by 42% (alemtuzumab, 13% vs. SC IFNB-1a, 20%; p=0.0084)[4]
- Notable adverse events associated with alemtuzumab in CARE-MS II included infusion-associated reactions, infections of predominantly mild-to-moderate severity, and secondary autoimmunity (mainly thyroid disorders and, less frequently, immune thrombocytopenia)[4]

OBJECTIVE

To evaluate the effects of alemtuzumab on relapse rate over time in patients who relapsed on a prior therapy (CARE-MS II; NCT00548405)

METHODS

Study Design

- Entry criteria included age 18–55 years, baseline Expanded Disability Status Scale (EDSS) score ≤5, MS symptoms onset within 10 years, active RRMS (≥2 relapses in prior 2 years and ≥1 in the prior year), and relapse on prior therapy (≥1 relapse during treatment with IFNB or glatiramer acetate after receiving that therapy for ≥6 months [prior treatment with other therapies was also permitted])
- Patients were randomized to receive alemtuzumab (12 mg/day intravenous [IV] once daily on 5 consecutive days at baseline and 3 consecutive days at Month 12) or SC IFNB-1a 44 µg 3 times weekly
- Relapse events required objective signs on examination (as assessed by blinded raters) that lasted ≥48 hours, were present at normal body temperature, and were adjudicated retrospectively by an independent, blinded, relapse adjudication committee
- Patients who completed the study were eligible to enroll in an extension study, during which all patients were treated with alemtuzumab 12 mg as needed, ie, re-treatment with alemtuzumab for those receiving alemtuzumab in the core CARE-MS II study or initial alemtuzumab treatment for patients initially treated with SC IFNB-1a

Statistical Analysis

- Treatment effects on relapse rate were compared using a proportional means model with robust variance estimation and covariate adjustment for geographic region
- The ARR was estimated using negative binomial regression with robust variance estimation and covariate adjustment for geographic region

RESULTS

Patients

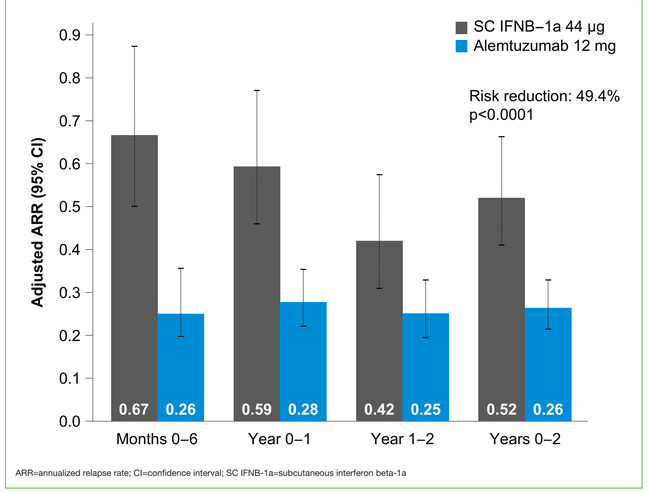
- A total of 667 patients were randomized and 628 were treated, receiving alemtuzumab 12 mg (n=426) and SC IFNB-1a (n=202)
- Treatment groups were balanced with regard to age, gender and race, as previously reported[4]

Relapse Rate

Co-primary Endpoint

- Over 2 years, the ARR was 0.26 (95% confidence interval [CI] 0.21–0.33) in the alemtuzumab 12-mg group and 0.52 (95% CI, 0.41–0.66) in the SC IFNB-1a group; the risk of a relapse was reduced by 49.4% in the alemtuzumab group compared with the SC IFNB-1a group over this time period (p<0.0001)[4]
- Alemtuzumab also reduced the relapse rate by 61% in the first 6 months (p<0.0001), 54% in Year 1 (p<0.0001) and 41% in Year 2 (p=0.0017) (**Figure 1**)

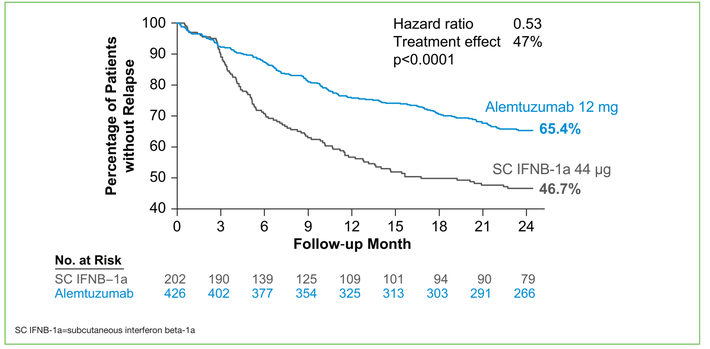
Figure 1. Annualized Relapse Rate by Year in CARE-MS II



ARR=annualized relapse rate; CI=confidence interval; SC IFNB-1a=subcutaneous interferon beta-1a

- Over 2 years, a significantly greater proportion of patients were relapse-free in the alemtuzumab 12-mg group compared with the SC IFNB-1a group (**Figure 2**)

Figure 2. Proportion of Relapse-free Patients

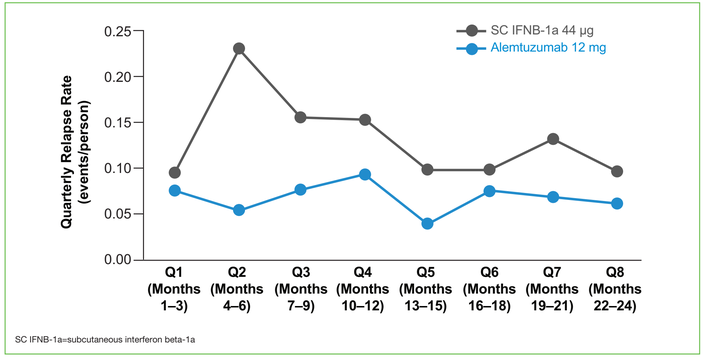


SC IFNB-1a=subcutaneous interferon beta-1a

Relapses by Quarter

- Analysis of relapse rates by quarter showed that alemtuzumab's effect on relapse reduction was apparent by the second quarter (Months 4-6) and was durable through to the final quarter of the 24-month study period (**Figure 3**)

Figure 3. Relapse Rate by Quarter



SC IFNB-1a=subcutaneous interferon beta-1a

- An interim analysis from the CARE-MS extension study demonstrated that alemtuzumab patients maintained a low relapse rate up to 36 months after initiating treatment, even without re-treatment during Year 3 in 80% of patients
- Alemtuzumab reduced the risk of severe relapses by 48% (p=0.012), by 56% for relapses treated with corticosteroids (p<0.0001), and by 55% for relapses that led to hospitalization (p=0.0045) compared with SC IFNB-1a[5]

CONCLUSIONS

- Alemtuzumab reduced the relapse rate more effectively than high-dose, high frequency SC IFNB-1a in active RRMS patients who had experienced disease activity on previous disease-modifying therapy
- The greater effect of alemtuzumab on relapse rate became apparent early (by the second quarter), with no increased risk toward the end of each 12-month period, and was durable throughout the 24-month study period
- Low relapse rate in alemtuzumab patients was maintained up to 36 months with most patients receiving 2 treatment courses over 3 years
- These results suggest that alemtuzumab has durability of effect

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