DX06

Efficacy of a Fourth Alemtuzumab Course in RRMS Patients With Disease Activity After Three Prior Courses: Analysis of CARE-MS II

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OBJECTIVE

- **To evaluate efficacy of a fourth course of alemtuzumab in CARE-MS II patients**

INTRODUCTION

- Alemtuzumab is approved in >65 countries for patients with RRMS, and is administered as 2 courses (Course 1: treatment initiation; Course 2: 12 months later)
  - The European Union Summary of Product Characteristics was recently updated to include 2 additional courses as needed (Courses 3 and 4)[1]
- In CARE-MS II (NCT00548405), alemtuzumab resulted in significantly greater improvements on clinical and MRI outcomes versus subcutaneous interferon beta-1a (SC IFNB-1a) over 2 years[2]
- The most frequent adverse events (AEs) with alemtuzumab were infusion-associated reactions (IARs); other AEs of interest included autoimmune AEs[2]
- Efficacy of alemtuzumab was maintained in a 4-year extension study (NCT00930553) in the absence of continuous treatment; 50% of patients did not receive additional alemtuzumab or other disease-modifying therapy (DMT) over 6 years after the initial 2 courses[3-5]
- The effects of alemtuzumab may be due to its selective depletion and distinct pattern of repopulation of circulating CD52-expressing T and B lymphocytes[6,7]
  - Following depletion, a relative increase in regulatory T cells and a decrease in proinflammatory cytokines occur, potentially leading to a rebalancing of the immune system[8,9]
  - The exact mechanism of action of alemtuzumab is not fully elucidated

METHODS

Patients and Treatment

- In CARE-MS II, patients with active RRMS and an inadequate response to prior therapy at core study baseline received 2 annual courses of alemtuzumab 12 mg/day IV (on 5 consecutive days at baseline and on 3 consecutive days 12 months later)[2]
- In the extension study, patients could receive additional treatment with alemtuzumab (12 mg/day on 3 consecutive days ≥12 months after the most recent course) as needed for relapse or MRI activity, or receive other licensed DMTs at the investigator's discretion[3]
  - Criteria for additional as-needed courses of alemtuzumab: ≥1 protocol-defined relapse, or ≥2 new/enlarging T2 hyperintense and/or new gadolinium (Gd)-enhancing T1 brain or spinal cord lesions on MRI
  - Disqualification criteria included (but were not limited to): pregnancy, diagnosis of immune thrombocytopenia (ITP), anti-glomerular basement membrane disease, and history of malignancy (except basal cell carcinoma)

Statistical Analyses

- Post hoc analyses were carried out on data through Year 6 (end of the fourth year of the extension study; cutoff date September 15, 2015)
- Analysis of yearly distribution of additional courses was based on all alemtuzumab-treated CARE-MS II patients
- Efficacy was evaluated in those who received Course 4 and met the following additional criteria:
  - Course 4 was received prior to Month 61 to allow for ≥1 year of follow-up after treatment
  - No other DMTs were received through Year 6
- Efficacy was evaluated over 24 months after Course 4
- Efficacy data for those who received a fifth course were censored from the time of Course 5 onward
- Safety was evaluated in those who received Course 3 prior to Month 61 and no other DMTs through Year 6

CONCLUSIONS

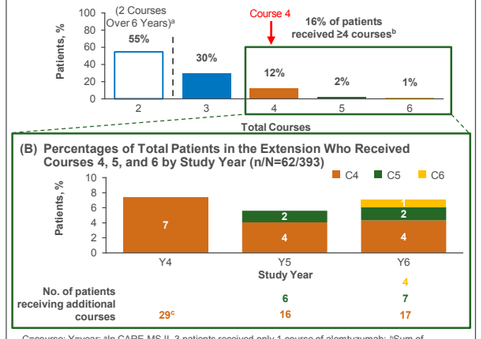
- **In the CARE-MS II extension study, 16% of patients received 4 or more courses of alemtuzumab for disease activity over 6 years; of these, the majority received only 4 courses**
  - **Mean time between Courses 3 and 4 was approximately 2 years**
- **Following a fourth course of alemtuzumab, relapse rates were significantly reduced and disability was stabilized or improved; these outcomes were sustained and clinically meaningful in the years following Course 4**
  - **The robustness of these results is supported by the high retention rate (79%) from CARE-MS II core study baseline through Year 6**
- **The safety profile of alemtuzumab in patients who received additional courses was similar to that observed in the overall CARE-MS II population and those who received 2 courses over 6 years**
- **These data support the administration of a fourth course of alemtuzumab to achieve disease control in patients with disease activity following Course 3**

RESULTS

Overall Patients and Additional Treatment

- 435 patients received alemtuzumab 12 mg in the CARE-MS II study, and 423 completed the core study; 393 entered the extension and 344 remained on study through Month 72 (Year 6)
  - 79% of patients remained on study from core study baseline through Year 6
- 62/393 (16%) patients who entered the extension received ≥4 courses of alemtuzumab through Year 6 (**Figure 1A**); of these, 49 (12%) received exactly 4 courses, and 13 (3%) received more than 4 courses
  - Most common reasons for receiving Course 4 included relapse (60%), MRI activity (15%), and both relapse and MRI activity (24%)
  - Course 4 was most frequently given in Year 4 (**Figure 1B**)
  - Mean time from Course 3 to Course 4 was 1.7 years (median [range]: 1.5 years [0.9–3.9])

Figure 1. CARE-MS II Patients Receiving Additional Alemtuzumab Courses Through Year 6



C=course; Y=year; [a]In CARE-MS II, 3 patients received only 1 course of alemtuzumab; [b]Sum of percentages differs due to rounding; [c]4 patients received Course 4 <12 months (Days 337, 351, 358, and 365) after Course 3

Efficacy and Safety Analysis Population

- Of the 62 patients who received ≥4 courses through Year 6, 43 (69%) received Course 4 before Month 61 and received no DMT
  - 18 of these patients completed at least 2 years of follow-up after Course 4
- Baseline characteristics in patients who received ≥4 courses were comparable to the overall CARE-MS II population and those who received 2 courses over 6 years, with the exception of a lower Gd-enhancing lesion count in the ≥4 courses group (**Table 1**)

Table 1. Baseline Characteristics in Alemtuzumab-Treated CARE-MS II Patients

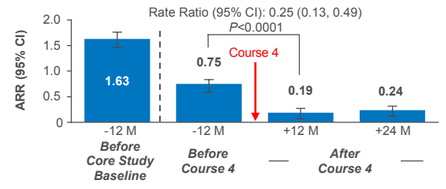
Parameter	Alemtuzumab 12 mg		
	Overall CARE-MS II Population (N=435)	Patients Receiving 2 Courses Over 6 Years[a] (N=192)	Patients Receiving ≥4 Courses[b] (N=43)
Age, years	34.7 (8.3)	35.4 (8.2)	34.2 (9.5)
Female, n (%)	287 (66.0)	117 (60.9)	22 (51.2)
White, n (%)	392 (90.1)	180 (93.8)	37 (86.0)
EDSS score	2.7 (1.3)	2.7 (1.1)	2.6 (1.3)
Years since initial relapse	4.5 (2.7)	4.4 (2.8)	4.4 (2.2)
No. of relapses in prior 1 year	1.7 (0.9)	1.7 (0.9)	1.7 (1.0)
No. of relapses in prior 2 years	2.8 (1.2)	2.7 (1.2)	2.9 (1.1)
Gd-enhancing lesion count	2.3 (6.0)	2.1 (4.9)	1.4 (3.0)
BPF	0.81 (0.02)	0.81 (0.02)	0.81 (0.02)

BPF=brain parenchymal fraction; EDSS=Expanded Disability Status Scale; [a]Patients in this subgroup received only the initial 2 courses of alemtuzumab in CARE-MS II, and no additional courses and no other DMT through 6 years; [b]Patients in this subgroup received no other DMT through 6 years and received Course 4 prior to Month 61
All values are mean (SD) unless indicated otherwise

Clinical Efficacy

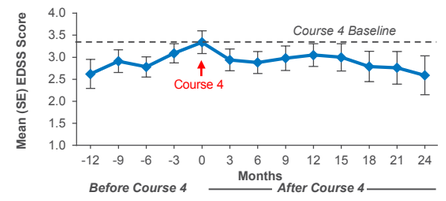
- Annualized relapse rate (ARR) declined significantly after Course 4 and remained low over the following 24 months (**Figure 2**)
- Mean EDSS score was stabilized after Course 4 (**Figure 3**)
- A majority of patients (68%) had EDSS scores that were stable/improved from core study baseline 12 months following Course 4
- All patients were free of 6-month confirmed disability worsening (CDW: ≥1-point EDSS increase from the most recent measurement prior to Course 4 [or ≥1.5 points if baseline EDSS=0] confirmed over 6 months) up to 24 months following Course 4
- 30% of patients achieved 6-month confirmed disability improvement (CDI) over 24 months following Course 4 (**Figure 4**)

Figure 2. ARR in Patients Who Received ≥4 Alemtuzumab Courses



M=month; ARR was estimated using a negative binomial model

Figure 3. Mean EDSS Score in Patients Who Received ≥4 Alemtuzumab Courses

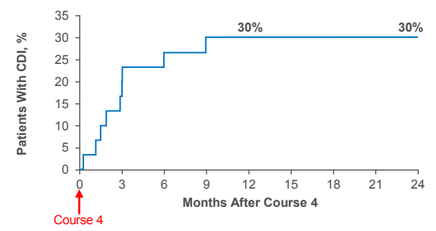


EDSS baseline is defined as the most recent measurement prior to Course 4

Safety of Any Additional Courses

- 144 patients received Course 3 prior to Month 61 and no other DMTs through Year 6
- No patients receiving additional courses of alemtuzumab withdrew from the extension study due to AEs, and no deaths were reported
- Incidences of AEs, including IARs, infections, and serious infections, were similar between patients who received additional courses and both the overall study population and patients who received 2 courses over 6 years (**Table 2**)
- There was no evidence of increased thyroid AEs among patients receiving additional courses; the incidence of thyroid AEs was numerically lower in the additional courses group compared with the 2 courses over 6 years group
- Two cases of ITP and no cases of nephropathy were reported among patients who received additional courses
- Incidence of malignancies was low and similar between both groups
  - Malignancy was reported in 2 patients receiving additional courses (Grade 2 squamous cell carcinoma and Grade 1 basal cell carcinoma)

Figure 4. Patients With 6-Month CDI After Receiving Course 4



CDI: ≥1-point EDSS decrease from the most recent measurement prior to Course 4 confirmed over 6 months; CDI is assessed only in patients with EDSS score ≥2.0 at the most recent measurement prior to Course 4; Kaplan-Meier estimates were used to assess proportions of patients with 6-month CDI

Table 2. AE Incidences in Alemtuzumab-Treated CARE-MS II Patients Through Year 6

	Alemtuzumab 12 mg		
	Overall CARE-MS II Population (N=435)	Patients Receiving 2 Courses Over 6 Years[a] (N=192)	Patients Receiving Any Additional Courses[b] (N=144)
Any AE, n (%)	433 (99.5)	191 (99.5)	144 (100)
Serious AEs	172 (39.5)	74 (38.5)	60 (41.7)
Infections	374 (86.0)	164 (85.4)	128 (88.9)
Serious infections	36 (8.3)	16 (8.3)	12 (8.3)
Autoimmune AEs[c]			
Thyroid AEs	179 (41.1)	90 (46.9)	61 (42.4)
Serious thyroid AEs	20 (4.6)	16 (8.3)	3 (2.1)
ITP	16 (3.7)	8 (4.2)	2 (1.4)
Nephropathies	1 (0.2)	0	0
Malignancies	7 (1.6)	4 (2.1)	2 (1.4)
IARs	397 (91.3)	171 (89.1)	135 (93.8)
Serious IARs	14 (3.2)	4 (2.1)	6 (4.2)

[a]Patients in this subgroup received only the initial 2 courses of alemtuzumab in CARE-MS II, and no additional courses and no other DMT through 6 years; [b]Patients in this subgroup received no other DMT through 6 years and received Course 3 prior to Month 61; [c]First occurrence of AE

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