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Incidence of Infusion-Associated Reactions Decreases With Subsequent Courses of Alemtuzumab: 5-Year Data From the CARE-MS Extension Study

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OBJECTIVE

- **To report on infusion-associated reactions (IARs) associated with alemtuzumab during 3 years of the ongoing CARE-MS extension study (5-year total follow-up)**

INTRODUCTION

- Alemtuzumab is a humanized anti-CD52 monoclonal antibody approved for the treatment of RRMS in >50 countries
- Alemtuzumab demonstrated greater improvements in clinical and MRI efficacy outcomes over SC IFNB-1a, with a consistent safety profile across clinical trials, in patients with active RRMS who were either treatment-naive (CARE-MS I, NCT00530348) or had an inadequate response (≥1 relapse) to prior therapy at baseline (CARE-MS II, NCT00548405)[1,2]
- In an ongoing extension study (NCT00930553), alemtuzumab showed durable efficacy on clinical and MRI outcomes through 5 years, even though 61% of patients did not receive alemtuzumab retreatment since Month 12 or other disease-modifying therapy (DMT)[3,4]
- The most frequent adverse events (AEs) with alemtuzumab were IARs; other AEs of interest included autoimmune AEs[1,2]
- In the CARE-MS core studies, IARs occurred in 90% of patients with alemtuzumab 12-mg infusion, and were mostly mild to moderate (3% serious)[5]
- In a previous interim analysis of the extension study (4 years of total follow-up), IARs associated with alemtuzumab retreatment were predominantly mild or moderate[6,7]
- Although the exact mechanism is unknown, treatment-related IARs may result from cytokine-release syndrome[8] involving target cell lysis and further recruitment of inflammatory cells[9,10]

METHODS

Study Design

- CARE-MS I and II were phase 3, randomized, head-to-head, rater-blinded, 2-year studies of alemtuzumab versus SC IFNB-1a (44 µg 3 times per week)[1,2]
  - Patients randomized to alemtuzumab 12 mg/day IV received 2 annual courses (on 5 consecutive days at baseline and on 3 consecutive days 12 months later)
- In the extension study, patients could receive alemtuzumab retreatment (12 mg on 3 consecutive days ≥1 year after the most recent course)[11]
  - Retreatment criteria were ≥1 protocol-defined relapse, or ≥2 new/enlarging T_2 hyperintense and/or new gadolinium-enhancing T_1 brain or spinal cord lesions on MRI
- Use of other DMTs was permitted at the investigator's discretion
- Methylprednisolone (1 g/day IV) was given on the first 3 days of each course

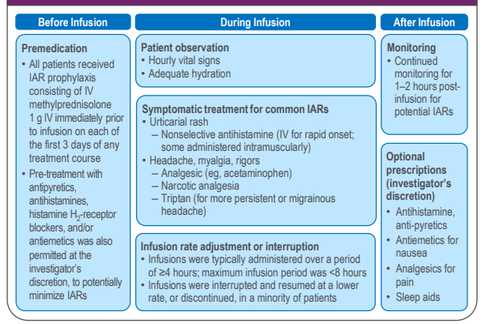
IAR Assessments and Treatment

- IARs were defined as any AE that occurred between the start of any alemtuzumab infusion and 24 hours after the end of the infusion
- IAR incidence was based on the number of treated patients in each treatment course
- IAR management included measures before, during, and after infusion (**Figure 1**)[6,7]

Statistical Analyses

- Interim analyses were based on pooled data from all available follow-up of patients treated with alemtuzumab 12 mg in CARE-MS I and II, and 3-year follow-up in the extension study (total 5-year follow-up from the first alemtuzumab dose)
- Data from all patients initially treated with alemtuzumab 12 mg in CARE-MS I or II, including those who transitioned into the extension study, were analyzed across both studies from the time of first alemtuzumab treatment

Figure 1. Management of IARs in the Alemtuzumab Clinical Trials



RESULTS

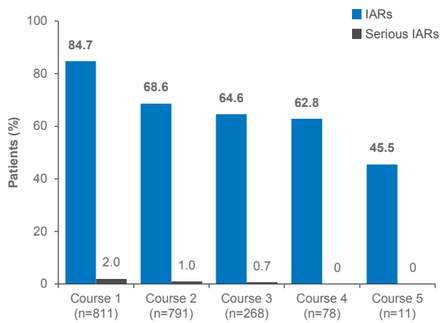
Patients

- A total of 811 patients received alemtuzumab 12 mg in the core studies; 742 (91.5%) entered the extension and, of those, 692 (93.3%) remained on study at Month 60 (Year 5)
  - Over the 5-year follow-up period, 453 (61.1%) patients received only the 2 initial courses of alemtuzumab in the core studies with no retreatment in the extension and no other DMT
    - 474 (63.9%) patients did not receive retreatment with alemtuzumab since the initial 2 courses at core study baseline and Month 12
    - 704 (94.9%) patients did not receive another DMT
  - 36.1% of patients who entered the extension received at least a third course of alemtuzumab (19.3% received Course 3 during Year 3, 9.4% during Year 4 and 7.4% during Year 5)
  - 10.5% of patients who entered the extension received at least a fourth course of alemtuzumab (6.1% received Course 4 during Year 4 and 4.4% during Year 5)
  - 25.6%, 9.0% and 1.5% received a total of 3, 4 and 5 courses over 5 years
    - CARE-MS I: 31.5% received >2 courses
    - CARE-MS II: 40.2% received >2 courses

IAR Incidence, Severity, and Type During Alemtuzumab Treatment Courses

- IARs were most frequent with the first alemtuzumab course (**Figure 2**)
- The incidence of serious IARs through Years 0–5 was low (3.2%)

Figure 2. IARs Were Most Frequent With the First Alemtuzumab Treatment Course



- IARs were mostly mild to moderate (**Table 1**)
- No IAR led to study withdrawal or death
- No IAR led to treatment withdrawal during Course 1, Course 4, or Course 5
  - 11 patients did not complete Course 1 due to IARs, but went on to complete Course 2
  - 6 patients (0.8%) and 1 patient (0.4%) permanently withdrew treatment due to IARs during Courses 2 and 3, respectively
    - IARs leading to treatment withdrawal included dyspnea and non-cardiac chest pain (n=1), chest discomfort and headache (n=1), allergic dermatitis, pharyngeal edema, purpura, rash and urticaria (all n=1)
- Among patients who received a third course, the incidence of IARs was 62.9% (0.7% serious) in those who received Course 3 during Year 3 (n=143), 71.4% (none serious) in those who received Course 3 during Year 4 (n=70) and 60.0% (1.8% serious) in those who received Course 3 during Year 5 (n=55)
  - The incidence of IARs was 71.1% (none serious) in those who received Course 4 during Year 4 (n=45), and 51.5% (none serious) in those who received Course 4 during Year 5 (n=33)

Table 1. IARs Were Mostly Mild or Moderate

Grade, n (%)	Course 1 (n=811)	Course 2 (n=791)	Course 3 (n=268)	Course 4 (n=78)	Course 5 (n=11)
1	456 (56.2)	318 (40.2)	101 (37.7)	31 (39.7)	4 (36.4)
2	531 (65.5)	378 (47.8)	136 (50.7)	33 (42.3)	4 (36.4)
3	39 (4.8)	20 (2.5)	4 (1.5)	1 (1.3)	0
4	2 (0.2)[a]	1 (0.1)[b]	0	0	0

[a]Angioedema (n=1) and atrial fibrillation (n=1); [b]Non-cardiac chest pain and dyspnea in the same patient

- The most common types of IARs were headache, rash, and pyrexia (**Table 2**)

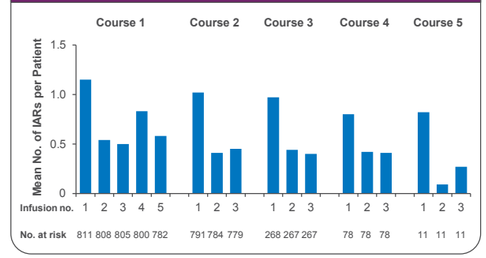
Table 2. IARs Occurring in ≥5% of Patients During Any Course

AE, n (%)[a]	Course 1 (n=811)	Course 2 (n=791)	Course 3 (n=268)	Course 4 (n=78)	Course 5 (n=11)
Rash	294 (36.3)	112 (14.2)	26 (9.7)	7 (9.0)	2 (18.2)
Headache	289 (35.6)	221 (27.9)	74 (27.6)	17 (21.8)	0
Pyrexia	124 (15.3)	104 (13.1)	37 (13.8)	8 (10.3)	2 (18.2)
Urticaria	95 (11.7)	35 (4.4)	10 (3.7)	4 (5.1)	0
Nausea	91 (11.2)	57 (7.2)	21 (7.8)	8 (10.3)	0
Pruritus	72 (8.9)	20 (2.5)	5 (1.9)	6 (7.7)	1 (9.1)
Flushing	58 (7.2)	33 (4.2)	12 (4.5)	8 (10.3)	1 (9.1)
Insomnia	56 (6.9)	33 (4.2)	11 (4.1)	2 (2.6)	0
Chills	47 (5.8)	30 (3.8)	10 (3.7)	1 (1.3)	0
Fatigue	46 (5.7)	28 (3.5)	9 (3.4)	2 (2.6)	0
Dyspnea	43 (5.3)	17 (2.1)	6 (2.2)	1 (1.3)	0
Rash generalized	41 (5.1)	28 (3.5)	4 (1.5)	3 (3.8)	0
Chest discomfort	40 (4.9)	23 (2.9)	10 (3.7)	2 (2.6)	1 (9.1)
Tachycardia	35 (4.3)	27 (3.4)	12 (4.5)	1 (1.3)	1 (9.1)
Pain	21 (2.6)	24 (3.0)	12 (4.5)	3 (3.8)	1 (9.1)

[a]Percentages based on number of treated patients in each course; a patient is counted only once within each preferred term

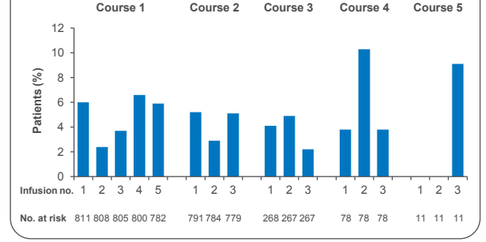
- Most IAR types decreased in incidence from Course 1 to Courses 4 and 5
- Serious IARs through Year 5 included pyrexia (n=3 [0.4%]), urticaria (n=3 [0.4%]), atrial fibrillation, nausea, chest discomfort, incorrect dose administered, headache, and hypotension (all n=2 [0.2%])
  - Incidences of serious Grade 3 or serious Grade 4 IARs were low (<1.0%) during each course
  - Anaphylaxis occurred in 1 patient, during Course 1
- The frequency of IARs was highest on the first infusion day of each course and generally decreased on subsequent infusion days (**Figure 3**)
- An increase in IARs was observed during the fourth infusion of Course 1, during which alemtuzumab was administered without prophylactic methylprednisolone, supporting the benefit of prophylactic use of corticosteroids to alleviate IARs

Figure 3. Frequency of IARs per Patient Was Highest With Initial Alemtuzumab Exposure



- Infusion interruption or adjustment occurred in a minority of patients (**Figure 4**)

Figure 4. A Minority of Patients Required Infusion Interruption or Adjustment



CONCLUSIONS

- **IARs were common with alemtuzumab, but decreased after Course 1 and were infrequently serious**
  - **Incidence was highest on Day 1 of each of Courses 1–5**
- **IARs were managed with pretreatment, patient education, appropriate symptomatic medication, monitoring, and adjustment of rate of infusion**

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CARE-MS=Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis.
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Alemtuzumab is approved in many countries around the world for treatment of adults with relapsing forms of MS. In the US, the indication provides that, because of its safety profile, the use of alemtuzumab should be reserved for patients who generally have had an inadequate response to 2 or more therapies indicated for the treatment of MS. In the EU, it is approved to treat patients with relapsing-remitting MS with active disease defined by clinical or imaging features. This material may contain information that is outside of the approved labeling in some countries.

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