Alemtuzumab in the treatment of multiple sclerosis: key clinical trial results and considerations for use

Eva Havrdova, Dana Horakova and Ivana Kovarova

Abstract: Alemtuzumab is a humanized monoclonal antibody therapy that has recently been approved in over 30 countries for patients with active relapsing-remitting multiple sclerosis. It acts by targeting CD52, an antigen primarily expressed on T and B lymphocytes, resulting in their depletion and subsequent repopulation. The alemtuzumab clinical development program used an active comparator, subcutaneous interferon beta-1a, to show that alemtuzumab is a highly efficacious disease-modifying therapy, with benefits on relapses, disability outcomes, and freedom from clinical disease and magnetic resonance imaging activity. The safety profile was consistent across studies and no new safety signals have emerged during follow-up in the extension study. Infusion-associated reactions are common with alemtuzumab, but rarely serious. Infection incidence was elevated with alemtuzumab in clinical studies; most infections were mild or moderate in severity. Autoimmune adverse events occurred in approximately a third of patients, manifesting mainly as thyroid disorders, and less frequently as immune thrombocytopenia or nephropathy. A comprehensive monitoring program lasting at least 4 years after the last alemtuzumab dose allows early detection and effective management of autoimmune adverse events. Further experience with alemtuzumab in the clinic will provide needed long-term data.

Keywords: alemtuzumab, disease-modifying therapy, efficacy, mechanism of action, multiple sclerosis, safety

Introduction

Alemtuzumab is a humanized monoclonal antibody therapy for relapsing-remitting multiple sclerosis (RRMS). It was granted licensing approval by the European Medicines Agency (EMA) in September 2013. This was followed soon afterwards by approval from regulatory authorities in several other countries. The indication varies across jurisdictions, being approved for the treatment of active RRMS defined by clinical or imaging features, for the treatment of active RRMS with inadequate response to interferon beta (IFNB) or other disease-modifying therapies (DMTs), or the treatment of relapsing forms of multiple sclerosis (MS). Approval by the US Food and Drug Administration (FDA) was initially denied owing to concerns about the design of the pivotal studies. Because patients were not blinded to treatment assignment, the FDA determined that the data were insufficient to demonstrate that the benefits of the treatment outweighed the risks

[Coles and Compston, 2014]. Effective patient blinding was not possible due to the high incidence of infusion-associated reactions (IARs) associated with the drug, but all efficacy assessments were performed by blinded neurologists. The application was resubmitted for consideration with additional data analyses. In November 2014, alemtuzumab was approved by the FDA for relapsing forms of MS, generally reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS [Genzyme Corporation, 2014]. It will be available through a restricted distribution program.

Multiple sclerosis

The pathogenesis of MS is not fully understood, but is associated with activation of autoreactive lymphocytes, which infiltrate the central nervous system (CNS) and mediate demyelination. Demyelination leaves axons susceptible to injury

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from the inflammatory environment [Compston and Coles, 2008; Keough and Yong, 2013]. Ultimately, axonal transection or neural death results in irreversible functional deficits.

Various lymphocyte populations have been implicated in demyelination. Interleukin (IL)-17–producing T cells have been observed in active MS lesions in the CNS. Under experimental conditions, they have been associated with breaking down the blood–brain barrier, killing neurons, interfering with neural stem cell proliferation and enhancing oligodendrocyte apoptosis [Kebir *et al.* 2007; Paintlia *et al.* 2011; Yamout *et al.* 2013]. Regulatory T cells function to suppress autoreactive T-cell proliferation in healthy individuals through cytokine production and contact with effector T cells or antigen-presenting cells [Zozulya and Wiendl, 2008]. In patients with MS, this suppressive function is impaired [Viglietta *et al.* 2004; Fletcher *et al.* 2009]. B lymphocytes also play a role in MS pathology. Clonally expanded B lymphocytes have been observed in MS lesions and normal-appearing white matter [Baranzini *et al.* 1999]. The precise function of B cells in MS pathogenesis is unknown but likely involves antigen presentation, cytokine production and/or immunoglobulin synthesis [Krumbholz *et al.* 2012].

Alemtuzumab pharmacodynamics and mechanism of action

Alemtuzumab targets CD52, an antigen of unknown function that is expressed on lymphocytes, monocytes, some dendritic cell populations and, to a lesser degree, on natural killer (NK) cells and other leukocytes (Figure 1) [Rao *et al.* 2012]. Alemtuzumab primarily depletes circulating T and B lymphocytes *via* antibody-dependent cytolysis and complement-dependent cytolysis. Antibody-dependent cytolysis predominates in the mouse model and is mediated by neutrophils and NK cells [Hu *et al.* 2009]. Human lymphocytes are also susceptible to complement-dependent cytolysis after alemtuzumab exposure, at least *in vitro* [Rao *et al.* 2012].

Depletion is followed by lymphocyte repopulation, which begins within weeks. B-lymphocyte counts typically return to baseline by 6 months post-treatment, whereas in clinical trials, mean T-cell counts approached normal (but not baseline) levels by 12 months post-treatment [Kovarova *et al.* 2012; Kasper *et al.* 2013]. CD4$^+$ T-cell repopulation is particularly delayed. In a long-term follow-up of 37 patients who had received alemtuzumab treatment in the 1990s for MS, median recovery time to normal levels was 8.4 months for B cells, 20 months for CD8$^+$ T cells and 12 years for CD4$^+$ T cells [Hill-Cawthorne *et al.* 2012]. It should be noted that many of these patients received a single treatment course of 100 mg over 5 infusion days, which is higher than the approved dose (60 mg over 5 days for the initial course, and 36 mg over 3 days for subsequent courses). T-lymphocyte repopulation is accomplished through proliferation of mature lymphocytes that escaped depletion (i.e. 'homeostatic' proliferation) as well as new production from precursors in the thymus [Cox *et al.* 2005; Jones *et al.* 2013].

Despite profound depletion of circulating lymphocytes, animal studies have shown that lymphocyte numbers in primary and secondary lymphoid organs are maintained [Hu *et al.* 2009]. Other aspects of the immune system are also unaffected by alemtuzumab, including innate immune cells, some T-cell subsets (tissue-resident effector memory T cells), plasma cells and serum immunoglobulin levels [Coles *et al.* 1999b; Clark *et al.* 2012; Turner *et al.* 2013].

The therapeutic effect of alemtuzumab is likely not solely a consequence of lymphocyte depletion, but also of repopulation features. Patients with and without breakthrough disease activity after alemtuzumab treatment did not differ in the kinetics of lymphocyte repopulation, suggesting that the nature of the repopulating lymphocytes is as important as lymphocyte numbers [Kousin-Ezewu *et al.* 2014]. During repopulation, the relative proportions of regulatory T cells and memory-phenotype T cells are increased, and the proportion of naive T cells is decreased [Cox *et al.* 2005; Zhang *et al.* 2013]. These effects are most marked at month 1 and the cells generally return to baseline proportions by month 12. Similarly, the relative proportions of B-cell subsets are also shifted after alemtuzumab treatment [Hartung *et al.* 2012; Kasper *et al.* 2013]. The proportion of B cells with a mature naive phenotype was reduced after treatment, whereas the immature cell fraction increased. By month 6, these proportions approached their baseline levels. The serum cytokine profile is also altered for at least 6 months post-treatment, with marked decreases in IL-17 and cytokines that promote IL-17 production, including IL-21 and IL-23 [Zhang *et al.* 2013]. There are also decreases in the proinflammatory cytokines IFN-γ, IL-12 and IL-27.
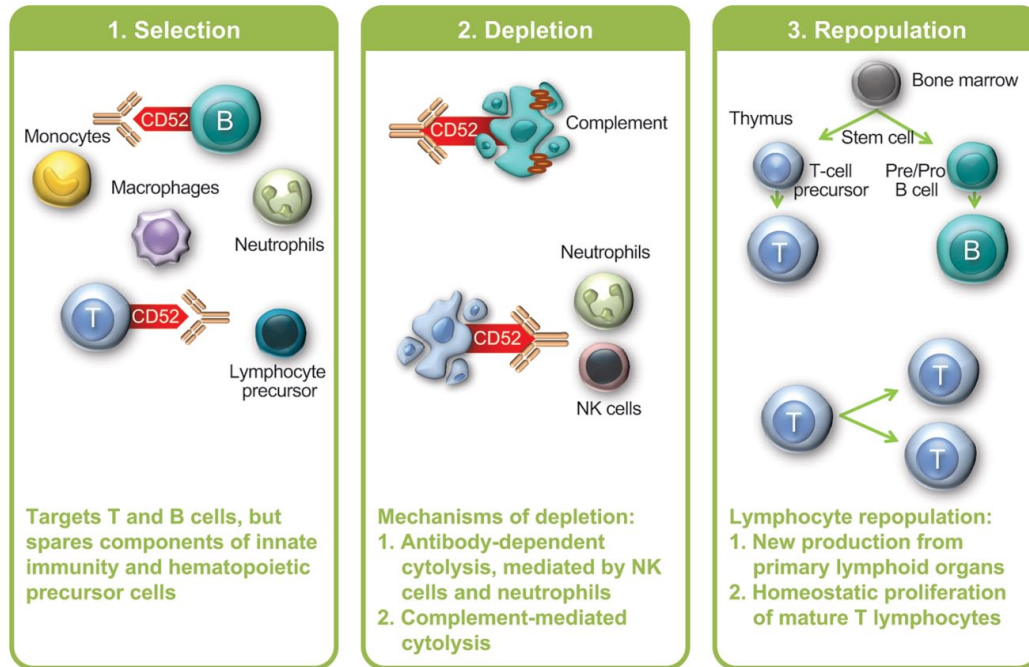
Figure 1. Alemtuzumab proposed mechanism of action.
NK, natural killer.

Development of alemtuzumab for MS

Alemtuzumab was initially developed as a treatment for B-cell chronic lymphocytic leukemia (B-CLL), and was approved for that use by the FDA and EMA in 2001. The dose used in the setting of B-CLL (30 mg/day 3 times weekly for 12 weeks) is considerably higher than that used for MS [Genzyme Corporation, 2007; Genzyme Europe, 2007].

The initial trial of alemtuzumab in MS focused on patients ($n = 28$) with secondary progressive disease [Coles *et al.* 1999b]. Despite effective suppression of inflammation, more than half the patients had a sustained increase in disability measured by the Expanded Disability Status Scale (EDSS) and/or had further brain volume loss during the 18-month follow-up period. These observations led to the hypothesis that, although axonal degeneration in patients with secondary progression occurs largely in the absence of inflammation, it is conditioned by the amount of prior inflammation-driven disease activity. The focus therefore shifted to treating patients earlier in their disease course. Patients with relapsing-remitting disease were targeted in the phase II and III studies.

Efficacy

Phase II

CAMMS223 [ClinicalTrials.gov identifier: NCT 00050778] was a randomized, rater-blinded, active-controlled, head-to-head trial of alemtuzumab *versus* subcutaneous (SC) IFNB-1a [CAMMS Trial Investigators *et al.* 2008]. Patients had early, active MS, defined as fulfilling the 2001 McDonald criteria [McDonald *et al.* 2001], $\geqslant 2$ relapses in the prior 2 years and $\geqslant 1$ gadolinium (Gd)-enhancing lesion, baseline EDSS score $\leqslant 3.0$, MS symptom onset within 3 years, and no prior immunotherapy for MS other than steroids. Alemtuzumab was administered by intravenous infusion on 5 consecutive days at baseline and on 3 consecutive days 12 months later (Figure 2). A third course at month 24 was available at the treating physician's discretion if the CD4$^+$ T-cell count was $\geqslant 100 \times 10^6$ cells/l. All patients received prophylaxis for IARs consisting of methylprednisolone 1 g/day on the first 3 days of infusion of each course; antihistamines and antipyretics were also permitted. Almost 3 years after the study start, alemtuzumab dosing was suspended after three reports of immune thrombocytopenia (ITP), including the fatal index case, but safety and efficacy assessments continued. Coprimary efficacy outcomes
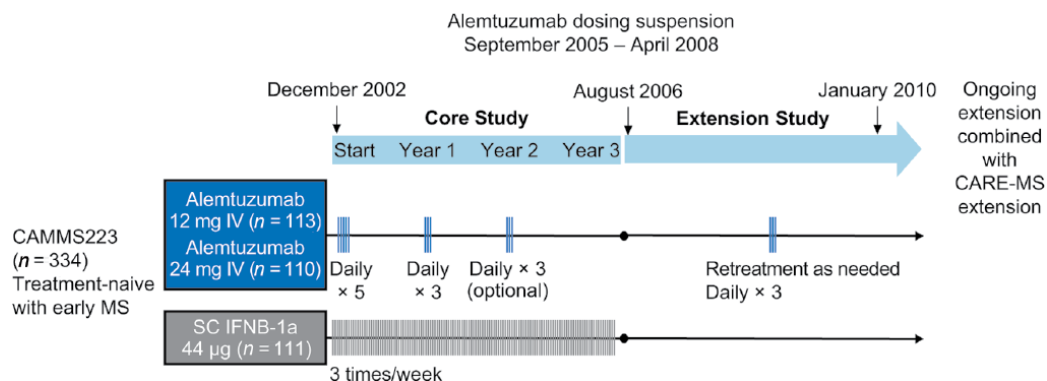
Figure 2. CAMMS223 phase II study design. Alemtuzumab was infused intravenously (IV) on 5 consecutive days at baseline and on 3 consecutive days at year 1. The third treatment course at year 2 was given at the discretion of the investigator if CD4+ T-cell counts were ≥100 × 10^6 cells/l. In the extension study, patients originally randomized to SC IFNB-1a were not eligible for alemtuzumab treatment, but could take other disease-modifying therapies. Patients originally randomized to alemtuzumab could receive alemtuzumab retreatment at any point during the extension after the dosing suspension was lifted and ≥12 months after the previous treatment course. Only the 12-mg dose was used for retreatment.
CARE-MS, Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis; IFNB, interferon beta; MS, multiple sclerosis; SC, subcutaneous.

were the time to sustained accumulation of disability (SAD) (≥1.5-point increase in EDSS score in patients with baseline score of 0 and ≥1-point increase for patients with baseline score of ≥1.0) confirmed over 6 months, and relapse rate.

Primary efficacy endpoints were met and have been reviewed elsewhere [Menge *et al.* 2014]. *Post hoc* analyses showed that at year 3, 73% of patients treated with alemtuzumab 12 mg were free of clinical disease activity, defined as an absence of 6-month SAD and relapse, compared with 43% in the SC IFNB-1a group (HR, 0.33; $p < 0.0001$) [Coles *et al.* 2011]. More alemtuzumab-treated patients also experienced a sustained reduction in disability, defined as a ≥1-point decrease in EDSS score sustained over a 6-month period in patients with baseline EDSS score ≥2.0 (45% *versus* 27% at year 3; $p = 0.01$) [Coles *et al.* 2011]. Median brain volume change from baseline to year 3 was −1.8% with SC IFNB-1a *versus* −0.9% with alemtuzumab 12 mg ($p = 0.16$).

Phase III
The Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis (CARE-MS) studies [ClinicalTrials.gov identifier: NCT00530348, NCT00548405] were 2-year, phase III, randomized, active-controlled, head-to-head trials (Figure 3) [Cohen *et al.* 2012; Coles *et al.* 2012b].

Although both CARE-MS studies enrolled patients with RRMS fulfilling the 2005 McDonald criteria [Polman *et al.* 2005] and active disease (defined as ≥2 relapses in the prior 2 years and ≥1 relapse in the prior year), their main point of differentiation was the treatment history of the target populations. In CARE-MS I, eligible patients had never received DMT, had a baseline EDSS score ≤3.0 and MS symptom onset within 5 years. In contrast, CARE-MS II patients were required to have relapsed on prior IFNB or glatiramer acetate treatment after receiving that therapy for ≥6 months (prior treatment with other therapies, including natalizumab, was also permitted). Additionally, they had to have baseline EDSS score ≤5.0 and MS symptom onset within 10 years. In both studies, patients were randomized 2:1 to two annual treatment courses of alemtuzumab 12 mg/day or SC IFNB-1a 44 μg three times weekly, with corticosteroid premedication on the first 3 days of each treatment course for IAR prophylaxis. In CARE-MS II, there was an additional alemtuzumab 24-mg treatment arm; however, randomization into this arm was discontinued early to increase enrollment in the 12-mg arm and it was deemed exploratory for statistical purposes.

The coprimary efficacy outcomes were relapse rate and time to 6-month SAD. Patient characteristics and primary efficacy results have been
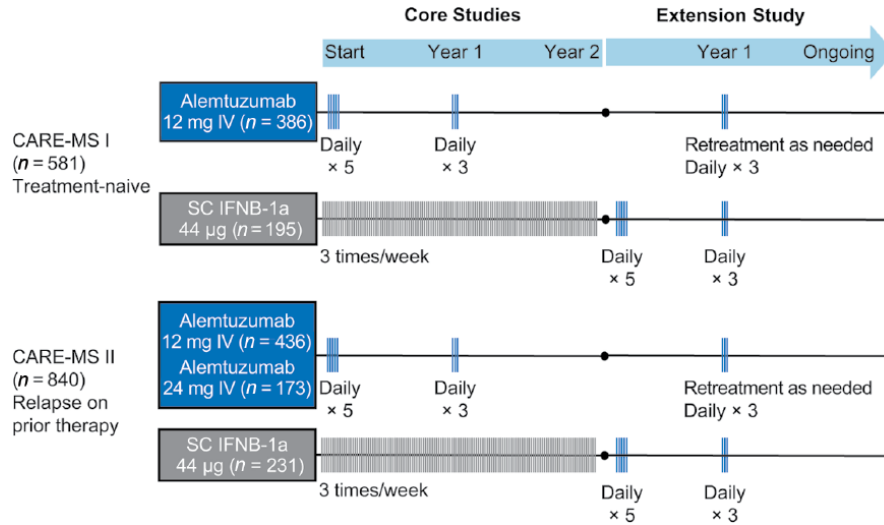
Figure 3. CARE-MS phase III study design. CARE-MS studies were 2-year, phase III, randomized, active-controlled, head-to-head trials. Both studies enrolled patients with active relapsing-remitting multiple sclerosis (defined as ≥2 relapses in the prior 2 years and ≥1 relapse in the prior year). In the extension study, patients originally randomized to subcutaneous interferon beta-1a (SC IFNB-1a) received two annual courses of alemtuzumab 12 mg. Patients originally randomized to alemtuzumab could receive alemtuzumab retreatment if they fulfilled magnetic resonance imaging (MRI) or relapse criteria (≥1 protocol-defined relapse in the previous year or ≥2 unique MRI lesions on brain or spinal cord). Retreatment could occur at any point during the extension ≥12 months after the previous treatment course. Only the 12-mg dose was used for retreatment. CARE-MS, Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis; IV, intravenous.

reviewed elsewhere [Menge *et al.* 2014]. Although the SAD endpoint was met in CARE-MS II, a statistically significant difference between alemtuzumab and SC IFNB-1a was not detectable in CARE-MS I. The inability to detect a treatment difference stemmed from the unexpectedly low rate of SAD in the SC IFNB-1a group. Power calculations for the study were based on CAMMS223 data; 20% of patients were expected to attain 6-month SAD with SC IFNB-1a rather than the observed 11%. In both studies, alemtuzumab 12 mg was superior to SC IFNB-1a in reducing relapses and increasing the proportion of patients who were free of clinical disease (absence of relapses and SAD), and the proportion free of magnetic resonance imaging (MRI) activity (Gd-enhancing and new/enlarging T_2 lesions) and clinical disease (Figure 4).

Long-term efficacy
All patients completing the phase II and III trials were eligible to continue in an ongoing extension study [ClinicalTrials.gov identifier: NCT 00930553] in which they could receive as-needed alemtuzumab retreatment. Retreatment rates in

the phase III program were 26−31% over 4 years of follow-up [Coles *et al.* 2014; Hartung *et al.* 2014]. In several long-term investigator-led studies ('the Cambridge cohort'; *n* = 87), this figure rose to 48% over up to 12 years of follow-up [Tuohy *et al.* 2014].

In a 5-year follow-up of the CAMMS223 extension, the risk of SAD from baseline to year 5 was reduced by 69% ($p = 0.0005$) in the alemtuzumab 12-mg group relative to the SC IFNB-1a group [Coles *et al.* 2012a]. The EDSS score improved or remained stable in 74% of alemtuzumab 12-mg patients from baseline to year 5 compared with 54% of SC IFNB-1a patients ($p = 0.014$), and relapses were reduced by 66% ($p < 0.0001$). From year 3 to year 5, there was a 56% relative reduction in relapse rate, but this failed to reach significance ($p = 0.09$).

The phase III extension study currently has preliminary data up to 4 years after alemtuzumab initiation [Coles *et al.* 2014; Hartung *et al.* 2014]. In this study, 349 patients enrolled from the CARE-MS I alemtuzumab group and 393 patients enrolled from the CARE-MS II

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