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Topical Review

Alemtuzumab: A new therapy for active relapsing–remitting multiple sclerosis

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Abstract: Alemtuzumab is a humanized monoclonal antibody directed against CD52 to deplete circulating T and B lymphocytes; lymphocyte depletion is followed by a distinctive pattern of T- and B-cell repopulation, changing the balance of the immune system. This review reports the efficacy and safety findings of the phase 2 CAMMS223 trial and the phase 3 CARE-MS I and II trials investigating alemtuzumab for the treatment of active relapsing–remitting MS. Alemtuzumab, administered intravenously, was shown to improve relapse rate versus subcutaneous interferon beta-1a in patients who were treatment-naive (CAMMS223 and CARE-MS I) or had relapsed on prior therapy (CARE-MS II), and to reduce sustained accumulation of disability (CAMMS223 and CARE-MS II). Important adverse events were infusion-associated reactions, serious infections and autoimmune events. A safety monitoring program allowed for early detection and management of autoimmune events. Recommendations for the monitoring of adverse events are made. Alemtuzumab's mechanism of action, pharmacodynamics and opportunities for future research are discussed.

Keywords: Alemtuzumab, multiple sclerosis, monoclonal antibody, CD52

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Introduction

Multiple sclerosis is a chronic and degenerative autoimmune inflammatory disease leading to demyelination and damage of axons in the brain and spinal cord.[1,2] Alemtuzumab is a humanized (immunoglobulin G1 (IgG1) isotype) monoclonal antibody that was recently approved in the European Union (EU), Australia and Latin America for adult patients with relapsing–remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features, and is also approved in Canada for patients who had an inadequate response to interferon-beta or other disease-modifying agents. It is directed against the glycoprotein CD52, a protein present on the surface of mature lymphocytes, and it depletes circulating T and B lymphocytes, thought to be critical mediators of MS.[3,4] After lymphocyte depletion, a distinctive pattern of T- and B-lymphocyte repopulation occurs over time, changing the balance of the immune system.[5,6]

In this review, trial results that are pertinent to its approval for the treatment of active RRMS are summarized. Recommendations for the monitoring of adverse events are made. Additionally, alemtuzumab's mechanism of action, pharmacodynamics and opportunities for future research are discussed.

Clinical findings

Phase 3 trials

The efficacy and safety of alemtuzumab in patients with RRMS was evaluated in two phase 3 studies, the Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis (CARE-MS) I (ClinicalTrials.gov number NCT00530348) and II (ClinicalTrials.gov number NCT00548405) studies (for an overview, see Table 1).[7,8] In both studies, patients were randomized to receive alemtuzumab (12 mg/day intravenous (IV) once daily for five consecutive days at baseline and for three consecutive days at 12 months) or a high-dose active comparator, subcutaneous interferon beta-1a (SC IFNβ-1a; Rebif®) 44 µg three times weekly (Figure 1). Efficacy assessments (clinical and magnetic resonance imaging (MRI)) were rater-blinded. While a double-blind trial model would be ideal in comparing therapies, it was decided at the design

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Table 1. Overview of key clinical trials investigating alemtuzumab vs an active comparator for the treatment of RRMS.

	CAMMS223[a] Primary analysis[10]		CAMMS223 Extension study[11]		CARE-MS I[7,9]		CARE-MS II[8,9]	
Study design	Randomized (1:1:1 alemtuzumab 12 mg IV vs alemtuzumab 24 mg IV vs SC IFNβ-1a 44 µg), rater-blinded, active-controlled, head-to-head				Randomized (2:1 alemtuzumab 12 mg IV vs SC IFNβ-1a 44 µg), rater-blinded, active-controlled, head-to-head		Randomized (2:1 alemtuzumab 12 mg IV vs SC IFNβ-1a 44 µg), rater-blinded, active-controlled, head-to-head[b]	
Study type	Phase 2				Phase 3		Phase 3	
Study duration, years	Three		Five		Two		Two	
Patient population	Active RRMS (defined as ≥2 relapses in the prior two years and ≥1 Gd^+ lesion); treatment-naive; EDSS ≤3; onset ≤3 years				Active RRMS (defined as ≥2 relapses in the prior 2 years and ≥1 relapse in the prior year); treatment-naive; EDSS ≤3; onset ≤5 years		Active RRMS (defined as ≥2 relapses in the prior 2 years and ≥1 relapse in the prior year); relapsing on prior DMT; EDSS ≤5; onset ≤10 years	
Co-primary endpoint results								
	SC IFNβ-1a (*n* = 111)	**Alemtuzumab 12 mg (*n* = 112)**	**SC IFNB-1a (*n* = 111)**	**Alemtuzumab 12 mg (*n* = 112)**	**SC IFNβ-1a (*n* =187)**	**Alemtuzumab 12 mg (*n* = 376)**	**SC IFNβ-1a (*n* = 202)**	**Alemtuzumab 12 mg (*n* = 426)**
ARR **Relative reduction vs SC IFNβ-1a**	0.36	0.11 69% ($p<0.001$)	0.35	0.12 66% ($p<0.0001$)	0.39	0.18 55% ($p<0.0001$)	0.52	0.26 49% ($p<0.0001$)
Patients with SAD, % **Relative reduction vs SC IFNβ-1a**	24	8 75% ($p<0.001$)	30	13 69% ($p=0.0005$)	11	8 NS	21.1	12.7 42% ($p=0.0084$)
Additional clinical efficacy outcomes								
Proportion of relapse-free patients, %	52	77	41	68	59	78 ($p<0.0001$)	47	65 ($p<0.0001$)
EDSS score change from baseline	+0.46	–0.32 ($p<0.001$)	+0.46	–0.15 ($p=0.014$)	No significant treatment difference		+0.24	–0.17 ($p<0.0001$)
Proportion of patients with SRD, %[c]	NA	NA	NA	NA	25	23 (HR=0.87) (p=NS)	13	29 (HR=2.57) ($p=0.0002$)
MSFC score change from baseline	NA	NA	NA	NA	+0.03	+0.11 ($p=0.011$)	–0.04	+0.08 ($p=0.0022$)

[a]During the phase 2 study, there was a temporary suspension of alemtuzumab dosing following the index case of immune thrombocytopenia (ITP), during which time safety and efficacy assessments proceeded as planned. Following the lifting of the dosing suspension, alemtuzumab treatment resumed with an optional alemtuzumab re-treatment course (12 mg/day on 3 consecutive days) being permitted at least 12 months after the last treatment course. [b]Randomization into a third treatment arm (alemtuzumab 24 mg) was discontinued early, and it was deemed exploratory for statistical purposes. [c]Post hoc SRD data for CAMMS223 are published elsewhere (Coles et al.[11]).

CARE-MS: Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis; ARR: annualized relapse rate; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; Gd+: gadolinium; HR: hazard ratio; IV: intravenous; MSFC: MS Functional Composite; NA: not available; NS: non-significant; RRMS: relapsing–remitting multiple sclerosis; SAD: sustained accumulation of disability; SC IFNβ-1a: subcutaneous interferon beta-1a; SRD: sustained reduction in disability. Adapted from Freedman et al.[15]

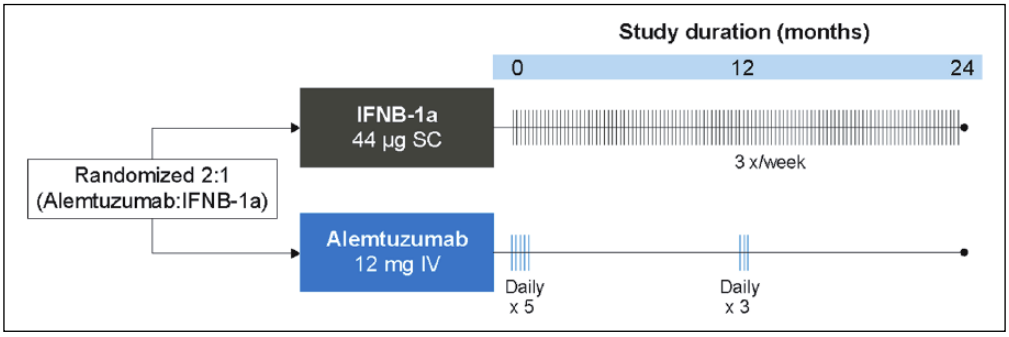

Figure 1. Trial design of CARE-MS I[7] and CARE-MS II.[8]
In CARE-MS II, randomization into a third treatment arm (alemtuzumab 24 mg) was discontinued early and deemed exploratory for statistical purposes. CARE-MS: Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis IFNβ-1a: interferon beta-1a; IV: intravenous; SC: subcutaneous.

stage that patient unblinding due to the distinct mode of administration and established side effect profile of the two therapies was inevitable in practice, and there were expressed concerns about the ethics and practicality of maintaining patients, well aware they had the active infused therapy, on over two years of thrice weekly subcutaneous injections.

All primary outcomes for the treatment of RRMS were reported versus SC IFNβ-1a; there were no placebo arms. The active comparator for these clinical trials, SC IFNβ-1a, has been shown to provide clinically meaningful benefit in patients with RRMS. In the SC IFNβ-1a pivotal clinical trials, SC IFNβ-1a demonstrated a reduction in relapse rate (33%), active T2 lesions (78%), and disability progression (30%) compared with placebo. This was among the most effective approved therapies at the time of the alemtuzumab clinical trial program.[9,12]

Eligibility rules for both studies required patients to have active disease defined as having experienced at least two relapses in the past two years, with at least one in the past year. In CARE-MS I, treatment-naive RRMS patients with an Expanded Disability Status Scale (EDSS) score ≤3.0 at baseline were included in the trial. Baseline characteristics included a mean age of 33 years, a mean time of two years since first symptoms and a mean EDSS score of 2.0.[7] CARE-MS II enrolled RRMS patients who had relapsed on prior therapy and had an EDSS score ≤5.0 at baseline.[8] At baseline, patients had a mean age of 35 years, a mean time since first symptoms of 4.5 years and a mean EDSS score of 2.7; the mean duration of exposure to prior MS therapies (one or more drug used) was 35 months and 30% had received ≥2 prior MS therapies. An additional third arm in CARE-MS II using double-dose alemtuzumab was terminated early because of slow recruitment. Efficacy findings were broadly in line with the 12 mg arm with no new safety signals and, as this dose has not been considered for approval, the results will not be discussed further in this review.

The primary outcome measures for CARE-MS I and II were the annualized relapse rate (ARR) over two years and the time to onset of sustained accumulation of disability (SAD) compared with SC IFNβ-1a, defined as an increase of at least one point on the EDSS from a baseline score ≥1.0 (≥1.5-point increase for patients with baseline EDSS score of 0) that was sustained for six months.

In CARE-MS I, alemtuzumab reduced the ARR by 55% ($p < 0.0001$) compared with SC IFNβ-1a (Table 1).[7,9] There was a 30% reduction in six-month SAD that did not reach statistical significance (alemtuzumab, 8% vs SC IFNβ-1a, 11%; $p = 0.22$), with the mean EDSS score change from baseline being –0.14 in both the alemtuzumab and the SC IFNβ-1a arms ($p = 0.97$). One potential contributor to this statistically non-significant finding may have been the lower-than-expected proportion of patients in the SC IFNβ-1a group who met the six-month SAD endpoint in CARE-MS I (i.e. 11%) compared with 20% at 24 months in the phase 2 study[11] (described in further detail below) on which the power calculations for CARE-MS I were in part based. One might also speculate that given the lower MRI T2 lesion load at baseline in CARE-MS I (median lesion volume 4.2 vs 8.5 cm^3 in the phase 2 study), these patients had a lesser probability of developing disability progression than patients in the phase 2 study.

In CARE-MS II, alemtuzumab reduced the ARR by 49% ($p < 0.0001$) and six-month SAD by 42% (alemtuzumab, 13% vs SC IFNβ-1a, 21%; $p = 0.0084$) over

two years (Table 1).[8,9] The mean EDSS score in alemtuzumab-treated patients was significantly reduced over two years, indicating an improvement in disability score, whereas the mean EDSS score for patients treated with SC IFNß-1a was significantly increased from baseline (alemtuzumab, –0.17 vs IFNβ-1a, +0.24; $p < 0.0001$). Compared with SC IFNß-1a-treated patients, alemtuzumab-treated patients were 2.6 times more likely to demonstrate a sustained reduction in preexisting disability (SRD) over six months (Kaplan-Meier estimate: 28.8% vs 12.9% (hazard ratio (HR) 2.57; $p = 0.0002$)). In both CARE-MS I and II, treatment effects on clinical endpoints were associated with significant effects on MRI measures of inflammation and disease progression. Alemtuzumab significantly reduced the proportion of patients with new or enlarging T2-hyperintense lesions and gadolinium-enhancing lesions, and also slowed the parenchymal brain volume loss (a measure of brain atrophy) compared with SC IFNβ-1a (Table 2). No treatment differences were observed in median volume change of T2-hyperintense lesions.[7–9]

Supportive analyses of the CARE-MS I and II datasets showed that fewer alemtuzumab-treated patients experienced severe relapses (CARE-MS I: 61% risk reduction, $p = 0.0056$; CARE-MS II: 48% reduction, $p = 0.0121$), or relapses that led to steroid treatment (CARE-MS I: 58% reduction, $p < 0.0001$; CARE-MS II: 56% reduction, $p < 0.0001$). Moreover, among alemtuzumab-treated patients experiencing relapses, there was a trend for reduced hospitalizations in the CARE-MS I study (29% reduction, $p = 0.34$) and a significant reduction in hospitalizations in the CARE-MS II study (55% reduction, $p = 0.0045$) compared with SC IFNβ-1a.[7,8]

An extension study (ClinicalTrials.gov number NCT00930553) investigating the long-term efficacy and safety of alemtuzumab in patients who completed either CARE-MS I or II is currently ongoing.

Phase 2 trial

In the phase 2 study CAMMS223 (ClinicalTrials.gov number NCT00050778), the efficacy of alemtuzumab was evaluated in treatment-naive patients with active RRMS, with patients being treated with either alemtuzumab 12 mg/day ($n = 108$) or 24 mg/day ($n = 108$) (administered once per day on five consecutive days at baseline and on three consecutive days at 12 months, and for some patients at 24 months or later as needed) or SC IFNβ-1a 44 µg ($n = 107$) administered three times per week.[10] Patients in the three-year CAMMS223 study then had the option to continue in an extension phase[11] (for an overview, see Table 1). Forty-one patients received three or more courses of alemtuzumab, of which 37 patients received three courses and four patients received four courses; 31 of the 41 patients received three or more courses during the re-treatment phase (37 to 58 months after last alemtuzumab course). At baseline, patients had an EDSS score ≤3.0, a time since first symptoms of ≤3 years, at least two clinical episodes of MS in the two years prior to the study, and one or more gadolinium-enhancing lesion. At three years, alemtuzumab 12 mg reduced the ARR by 67% (HR, 0.33 (95% confidence interval (CI): 0.20–0.55), $p < 0.0001$) and the six-month SAD by 76% (HR, 0.24 (95% CI: 0.11–0.55), $p < 0.001$) compared with SC IFNβ-1a. These significant reductions in ARR and SAD were maintained after five years of follow-up.[11] During the five-year follow-up period, 41.7% of patients received re-treatment with three or more courses of alemtuzumab.

Considering freedom from clinical disease activity,[13] an increasingly reported efficacy criterion in MS trials defined as absence of both relapse and SAD (confirmed at six months in this study), a post hoc analysis of the CAMMS223 study showed that at three years, 73% of patients treated with alemtuzumab 12 mg were free from clinical disease activity compared to only 43% of patients treated with SC IFNβ-1a ($p > 0.0001$).[14]

Pooled safety analysis

A total of 1188 patients with RRMS treated with alemtuzumab (12 mg ($n = 919$) or 24 mg ($n = 269$)) constituted the safety population in a pooled analysis of data from CARE-MS I, CARE-MS II and CAMMS223, resulting in 2363 patient-years of follow-up and a median follow-up of 24 months (Table 3). Important adverse events were infusion-associated reactions (IARs), serious infections and autoimmune adverse events (thyroid disorders (including thyroid cancers), immune thrombocytopenia (ITP), nephropathies and cytopenias) and these are discussed in more detail in the *Management* section below.

Mechanism of action of alemtuzumab

The mechanism by which alemtuzumab exerts its clinical effects in MS has not been fully elucidated. Alemtuzumab selectively targets CD52, a cell surface antigen present at high levels on T ($CD3^+$ and $CD4^+$ or $CD8^+$), B ($CD19^+$) lymphocytes and monocytes (Figure 2), whose function remains unknown. In contrast, little or no CD52 is detected on cells of the

Table 2. MRI and disease-free survival endpoints from CARE-MS I and II.

	CARE-MS I[7,9] (Treatment-naive patients)			**CARE-MS II**[8,9] (Patients with inadequate response to prior therapy)		
	SC IFNβ-1a ***(n = 187)***	**Alemtuzumab 12 mg** ***(n = 376)***	***p* value**	**SC IFNβ-1a** ***(n = 202)***	**Alemtuzumab 12 mg** ***(n = 426)***	***p* value**
MRI						
Median change in volume of T2-hyperintense lesions	–6.5%	–9.3%	0.31	–1.2%	–1.3%	0.14
Patients with new or enlarging T2-hyperintense lesions through Year 2[a]	58%	49%	0.04	68%	46%	<0.0001
Patients with gadolinium-enhancing lesions through Year 2[a]	27.0%	15.4%	0.001	34.2%	18.5%	<0.0001
Patients with new T1 hypointense lesions through Year 2[a]	31.4%	24.0%	0.055	38.0%	19.9%	<0.0001
Median change in brain parenchymal fraction[a]	–1.488%	–0.867%	<0.0001	–0.810%	–0.615%	0.012
Disease-free survival						
Patients clinically disease free[a]	56%	74%		41%	60%	
Odds ratio (95% CI)		2.36 (1.62 to 3.43)	<0.0001		2.14 (1.52 to 3.01)	<0.0001
Patients MRI and clinically disease-free[a]	27%	39%		14%	32%	
Odds ratio (95% CI)		1.75 (1.17 to 2.61)	0.006		3.03 (1.89 to 4.86)	<0.0001

[a]Prespecified tertiary endpoint. CARE-MS: Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis; CI: confidence interval; MRI: magnetic resonance imaging; SC IFNβ-1a: subcutaneous interferon beta.

Table 3. Adverse reactions observed in >0.5% of patients treated with alemtuzumab 12 mg in a pooled analysis of data from CARE-MS I, CARE-MS II and CAMMS223 up to 24 months.[7–10]

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)
Infections and infestations	Upper respiratory tract infection, urinary tract infection	Lower respiratory tract infection, herpes zoster, gastroenteritis, oral herpes, oral candidiasis, vulvovaginal candidiasis, influenza, ear infection	Tooth infection, genital herpes, onychomycosis
Blood and lymphatic system disorders	Lymphopenia, leukopenia	Lymphadenopathy	Immune thrombocytopenia, thrombocytopenia, decreased hemoglobin, decreased hematocrit
Immune system disorders		Cytokine release syndrome	
Endocrine disorders		Graves' disease, hyperthyroidism, autoimmune thyroiditis, hypothyroidism, goiter, anti-thyroid antibody positive	
Psychiatric disorders		Insomnia[a], anxiety	Depression
Nervous system disorders	Headache[a]	MS relapse, dizziness[a], hypoesthesia, paresthesia, tremor, dysgeusia[a]	Sensory disturbance, hyperesthesia
Eye disorders		Blurred vision	Conjunctivitis, acute epitheliopathy of the retina[b]
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		Tachycardia[a], bradycardia, palpitations	
Vascular disorders	Flushing[a]	Arterial hypotension[a] and hypertension	
Respiratory, thoracic and mediastinal disorders		Dyspnea[a], cough, epistaxis, oropharyngeal pain	Throat tightness, hiccups, throat irritation, hypersensitivity pneumonitis[b]
Gastrointestinal disorders	Nausea[a]	Abdominal pain, vomiting, diarrhea, dyspepsia[a], stomatitis	Constipation, gastroesophageal reflux disease, gingival bleeding, dysphagia
Hepatobiliary disorders			Aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	Urticaria,[a] rash,[a] pruritus[a]	Generalized rash[a], erythema, ecchymosis, alopecia, hyperhidrosis, acne	Blister, night sweats
Musculoskeletal and connective tissue disorders		Myalgia, muscle weakness, arthralgia, back pain, pain in extremity, muscle spasm, neck pain	Undifferentiated connective tissue disorder[b]
Renal and urinary disorders		Proteinuria, hematuria	
Reproductive system and breast disorders		Menorrhagia, irregular menstruation	Cervical dysplasia, amenorrhea
General disorders and administration site conditions	Pyrexia[a], fatigue[a]	Chest discomfort[a], chills[a], pain[a], peripheral edema, asthenia, influenza-like illness, malaise, infusion site pain	Angioedema[a]
Injury, poisoning and procedural complications		Contusion	

[a]Adverse reactions reported as infusion-associated reactions. [b]Adverse events reported as autoimmune disorder (acute epitheliopathy of the retina ($n = 1$), hypersensitivity pneumonitis ($n = 2$), and undifferentiated connective tissue disorders ($n = 2$).

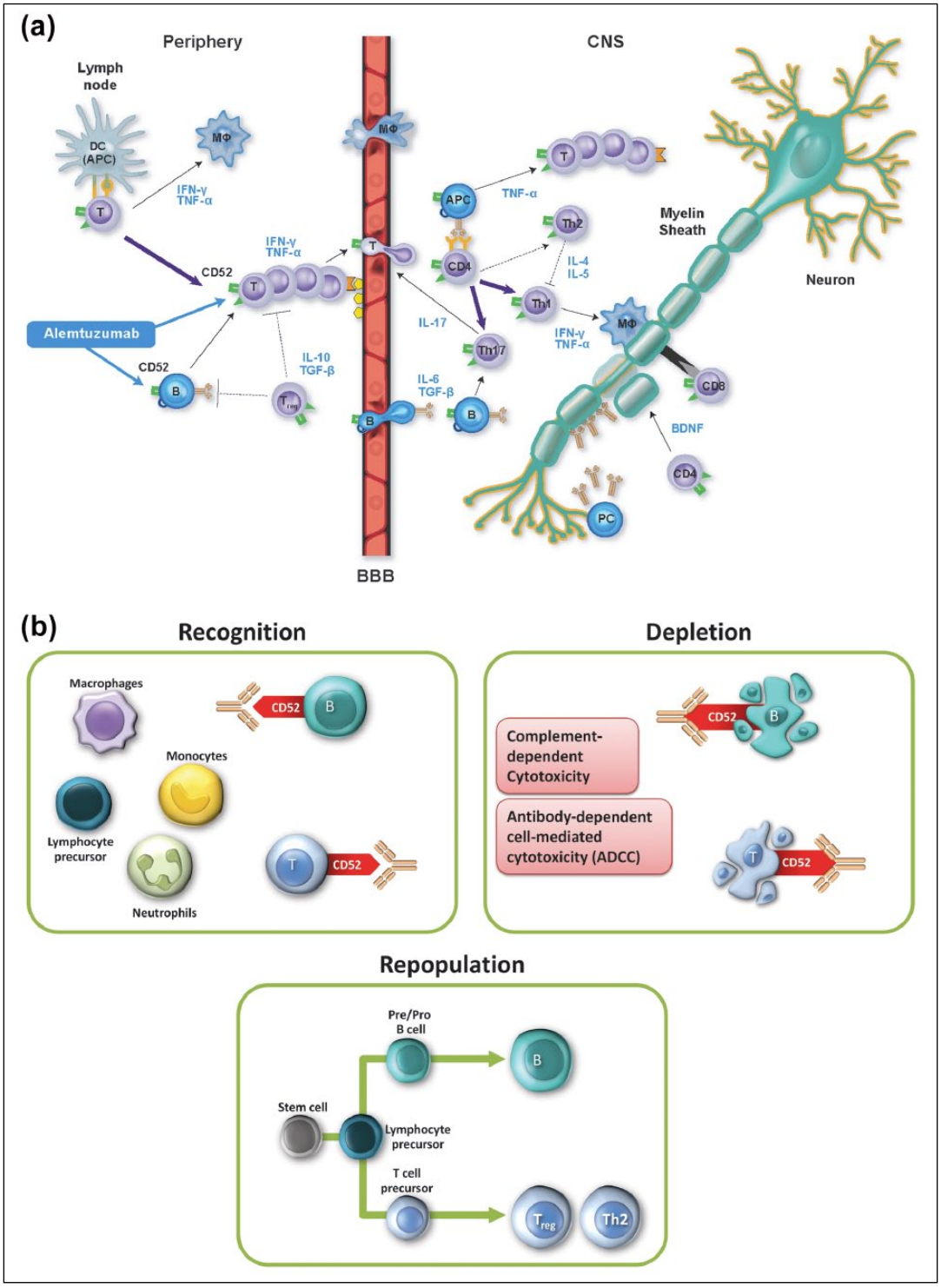

Figure 2. Mechanism of action of alemtuzumab.
(a) Cellular targets of alemtuzumab during the complex immunopathogenesis underlying MS. APC: antigen-presenting cell; B: B cell; BBB: blood-brain barrier; BDNF: brain-derived neurotrophic factor; CNS: central nervous system; DC: dendritic cell; IFN-γ: interferon-γ; IL: interleukin; PC: plasma cell; T: T cell; Th: T-helper cell; Treg: regulatory T-cell; TGF-β: transforming growth factor-β; TNF-α; tumor necrosis factor-α. Adapted with permission from Linker RA, Kieseier BC and Gold R. Identification and development of new therapeutics for multiple sclerosis. *Trends Pharmacol Sci* 2008; 29: 558–565, Copyright Elsevier 2008. (b) Suggested phases of alemtuzumab actions. The humanized monoclonal antibody alemtuzumab recognizes the CD52 antigen whose function is elusive on both T and B lymphocytes. By both complement-mediated and antibody-dependent cytotoxic macrophage-mediated mechanisms these cells are destroyed. Recovery of T and B cell populations occurs with different kinetics, B cells returning much earlier in peripheral blood. The repopulating T cell population is enriched in T regulatory cells that silence or diminish the impact of pathogenic autoreactive T cells.

innate immune system, e.g. neutrophils and natural killer cells.[15–17]

Alemtuzumab causes antibody-dependent cellular cytolysis and complement-mediated lysis following cell binding to the surface of T and B lymphocytes. Current evidence suggests immunomodulatory effects through the depletion and repopulation of lymphocytes,[6] including alterations in the number, proportion, and properties of certain lymphocyte subsets;[18,19] increased representation of regulatory T-cell subsets;[5] an increased representation of memory T lymphocytes; and rapid cell cycling of repopulating T cells with enhanced T-cell apoptosis.[15]

The initial decrease in the level of circulating T and B lymphocytes by alemtuzumab, coupled with a distinctive temporal (early B-cell and monocyte recovery, delayed T-cell recovery) and qualitative pattern of repopulation, is believed to have an anti-inflammatory effect and induces a change in the disturbed balance of the immune system that diminishes the potential for future relapse and disease progression.[19]

Pharmacodynamics of alemtuzumab

In an analysis investigating a population of 216 patients with RRMS, alemtuzumab concentrations decreased to low or undetectable levels within one month after dosing; however, its pharmacodynamic effect lasted considerably longer.[20] Each treatment course of alemtuzumab depletes circulating T and B lymphocytes, with the lowest observed values occurring at the earliest post-treatment time point (one month after a course of treatment in the above-mentioned phase 3 studies). Lymphocytes repopulate over time, with B-cell recovery being usually complete within six months, whereas T-lymphocyte counts rise more slowly and generally do not return to baseline by 12 months post-treatment. In the CARE-MS studies, approximately 40% of patients had total lymphocyte counts reaching the lower limit of normal (LLN) by six months after each treatment course, and approximately 80% of patients had total lymphocyte counts reaching the LLN by 12 months after each course.[7,8]

Future research

There is a conjecture that the clinical improvement seen is beyond a simple anti-inflammatory effect,[18] as is suggested by a post hoc analysis of CAMMS223 that demonstrated a sustained reduction of preexisting disability in a subgroup of patients who had no clinical disease activity immediately prior (<3 months) to alemtuzumab treatment. Furthermore, in a prespecified analysis of the CARE-MS II trial data, significant improvement in preexisting disability was seen in patient cohorts both with and without recent pretreatment relapses (<3 months) prior to alemtuzumab therapy.[21]

Additional evidence supporting the notion that alemtuzumab may confer neuroprotective effects[18] comes from brain MRI studies in CARE-MS patients, in which the decrease of the brain parenchymal fraction, as a measure of brain atrophy, was reduced by 42% (CARE-MS I) and 23% (CARE-MS II) in alemtuzumab-treated patients vs SC IFNβ-1a over two years ($p < 0.0001$ and $p = 0.012$, respectively).[7–9] It remains to be determined whether this effect reflects a strong anti-inflammatory action that limits the collateral damage to neurons or is indicative of an independent primary neuroprotective activity.[18]

In this context brain MRI studies investigating alemtuzumab's regional and temporal effects on gray and white matter atrophy as outcome measures may yield important further insights.

Management

Alemtuzumab has a well-characterized safety and tolerability profile, with a safety monitoring program that allows for early detection and management of adverse events.[7,8,10] Adverse events of interest include IARs, serious infections and autoimmune adverse events, including thyroid disorders and, less frequently, ITP and nephropathies.[7,8,10]

IARs

In the CARE-MS studies described above, IARs were defined as any adverse event occurring during or within 24 hours of alemtuzumab infusion. Most patients treated with the monoclonal antibody in this trial setting experienced mild to moderate IARs following administration of alemtuzumab 12 mg, most commonly headache, rash, nausea and pyrexia. Serious reactions occurred in 3% of patients.[7–9] Cardiac alterations such as tachycardia, bradycardia and palpitations have been reported among alemtuzumab-treated patients with MS (Table 3), of which serious adverse events were uncommon, symptoms resolved, and did not preclude alemtuzumab treatment.

It is recommended that patients be premedicated with corticosteroids immediately prior to the administration of alemtuzumab on each of the first three days of any treatment course to diminish IARs (Table 4).[7–9] In the CARE-MS trials, IARs were effectively managed

Table 4. Risk-management strategies adopted in core alemtuzumab clinical studies and recommended for clinical practice.[9].

Risk	Protocol risk-minimization measures	Included in study			Risk-management plan (RMP) for clinical practice
		CAMMS223	CARE-MS I	CARE-MS II	
IARs	Corticosteroids	Yes	Yes	Yes	Immediately prior to alemtuzumab administration on each of the first three days of any treatment course
	Antihistamines and/or antipyretics at investigator's discretion				Prior to alemtuzumab administration and as needed for symptomatic relief
Infections	Herpes prophylaxis	No[a]	Yes[b]	Yes[c]	Starting on first day of any treatment course continuing for a minimum of one month following the last infusion
Thyroid disorders	Thyroid function tests	Yes[b]	Yes	Yes	Prior to initiating alemtuzumab treatment and every three months until 48 months after last infusion
	Investigator and patient education				Investigator and patient education
ITP	Monthly CBC testing with differential	Yes[b]	Yes	Yes	Prior to initiating alemtuzumab treatment and monthly until 48 months after last infusion
	Monthly symptom monitoring survey (within 2 weeks of CBC test)				Not recommended in the RMP, because the survey's added value was not established in the trials
	Investigator and patient education				Investigator and patient education
Anti-GBM disease	Serum creatinine	Yes[d]	Yes[d]	Yes[d]	Prior to initiating alemtuzumab treatment and monthly until 48 months after last infusion
	Urinalysis with microscopy				Prior to initiating alemtuzumab treatment and monthly until 48 months after last infusion
	Monthly symptom-monitoring survey				Not recommended in the RMP, because the survey's added value was not established in the trials

[a]Implemented in Protocol Amendment 10; however, no patients in CAMMS223 received acyclovir prophylaxis. [b]Implemented in Protocol Amendment 3. [c]Implemented in Protocol Amendment 2. [d]Quarterly serum creatinine was in place from beginning of studies CAMMS223, CARE-MS I, and CARE-MS II; monthly testing was implemented in Protocol Amendment 10 for CAMMS223, Amendment 3 for CARE-MS I, and Amendment 2 for CARE-MS II.

CARE-MS: Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis; IAR: infusion-associated reaction; ITP: immune thrombocytopenia; CBC: complete blood count; anti-GBM: anti-glomerular basement membrane.

with methylprednisolone, antipyretics and antihistamines (Table 4).

Infections

As might be expected from alemtuzumab's mechanism of action, infections occurred more frequently with alemtuzumab 12 mg compared with SC IFNβ-1a in the CARE-MS trials (71% vs 53%, respectively), but were predominantly mild to moderate in severity.[7,8] Infections that occurred more often in alemtuzumab-treated patients than SC IFNβ-1a–treated patients included oral herpes, herpes zoster, nasopharyngitis, urinary tract infection, upper respiratory tract infection, sinusitis, influenza, bronchitis, and localized superficial (noninvasive) fungal infections. One case of esophageal candidiasis was reported as a serious adverse event and resolved with conventional treatment.[9] Two cases of active tuberculosis occurred with alemtuzumab. Both tuberculosis cases were from regions of known endemicity, and resolved with conventional antituberculosis treatment.[8] One patient with listeria meningitis responded to parenteral antibiotics and was discharged from hospital 15 days later, without sequelae, except fatigue. The patient received a second course of alemtuzumab 24 mg without infectious complication.[10] The relatively rare occurrence of serious infections may be consequent on the preservation of alemtuzumab-treated patients to mount protective B- and T-cell responses. This was shown in a case-control study of 24 patients in whom T-cell-dependent and T-cell-independent and antibody responses were recorded following vaccination with multiple bacterial and viral antigens.[22]

Prophylaxis with an oral anti-herpes agent should be initiated starting on the first day of alemtuzumab treatment and continuing for a minimum of one month following each course of treatment. In the CARE-MS program, patients received oral acyclovir 200 mg twice daily during alemtuzumab infusion and for 28 days thereafter as prophylaxis against herpes infections (Table 4).[7,8] Supportive data suggest that this prophylactic treatment following each alemtuzumab course is effective in reducing the risk of herpetic infections.[23]

Autoimmune adverse events

Treatment with alemtuzumab has been shown to increase the risk of autoimmune-mediated conditions including thyroid disorders, ITP or, rarely, nephropathies such as Goodpasture disease with anti-glomerular basement membrane (anti-GBM) antibodies. One potential mechanism for this may be a link between homeostatic T-cell proliferation following alemtuzumab-mediated lymphocyte depletion and lymphopenia-associated autoimmunity.[24,25] As autoimmune adverse events may occur months to years after alemtuzumab treatment, monitoring for these side effects until 48 months after the last alemtuzumab infusion is imperative.

Autoimmune thyroid disorders have been observed in 34.2% of RRMS patients treated with alemtuzumab in the phase 2 CAMMS223 study with a median follow-up of 57.3 months following first alemtuzumab exposure (including hyperthyroidism or hypothyroidism).[26] Extended follow-up revealed an onset of thyroid disease occurring between six and 61 months after the *first* treatment course, peaking in the third year post-treatment and declining thereafter.[12] In three years of follow-up following the first course of alemtuzumab in the phase 3 program, the incidence of first thyroid adverse events was higher in Year 3 (20.5%) than in the first two years of the core studies (16.9%), consistent with experience in the CAMMS223 study.[27] Most events were mild to moderate in severity. At three-year follow-up, the cumulative incidence of serious thyroid events (cancer, Grave's requiring radioiodine treatment) was 2.5%. Most thyroid events were managed with conventional medical therapy. However, some patients required surgical intervention (in the CARE-MS trials, three patients underwent thyroidectomy) and two patients received radioiodine ablation.[27] Thyroid function tests, such as the measurement of thyroid-stimulating hormone levels, should be obtained prior to initiation of treatment and every three months thereafter until 48 months following the last infusion (Table 4).

Based on the full safety experience up to November 26, 2012, the most common malignancies reported in alemtuzumab patients were thyroid cancer, breast cancer, basal cell carcinoma, and melanoma. Five cases of thyroid malignancies have been reported in alemtuzumab-treated patients.[7,8] All five thyroid malignancies occurred in patients who developed a thyroid disorder during the study (entry into which may itself be a risk factor for ascertainment of thyroid malignancies) and were discovered as incidental findings based on ultrasound examinations (a potential ascertainment bias). Although there was no evidence of increased risk of malignancy in alemtuzumab-treated MS patients, further study is needed to determine whether alemtuzumab raises the risk of malignancy.

Serious events of ITP have been observed in approximately 1% of patients treated with alemtuzumab in

the CARE-MS program, between 14 and 36 months after first exposure to alemtuzumab.[7,8] The first case of ITP, in the phase 2 CAMMS223 trial, went unrecognized and the patient died from intracerebral hemorrhage.[28] Following this index case, a monitoring program was implemented to identify and manage ITP systematically, including education on signs and symptoms for patients and physicians and monthly blood monitoring. Other autoimmune cytopenias, such as neutropenia, hemolytic anemia, agranulocytosis and pancytopenia, have been reported in the CARE-MS trials with lower incidence than ITP.[7,8] One patient experienced a recurrence of pancytopenia, which was associated with lack of compliance with corticosteroid therapy, resulting in fatal sepsis 20 months post-alemtuzumab treatment. It is recommended that complete blood counts with differential be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion (Table 4); if ITP or other cytopenia is suspected, a complete blood count should be obtained immediately, and if confirmed, the patient should be transferred for urgent care by a specialist.

Nephropathies, including anti-GBM disease, have been observed in 0.3% of patients in the clinical trial program and generally occurred within the recommended 48-month monitoring period following the last administration of alemtuzumab. In clinical trials, there were two cases of anti-GBM disease and two cases of membranous glomerulonephritis, identified early through clinical and laboratory monitoring.[29–31] Although these cases were serious, there was a positive outcome in renal function after treatment (normalization of serum creatinine and/or decreased proteinuria). Improvements in renal function were observed in both cases of anti-GBM disease after treatment with plasmapheresis, cyclophosphamide and glucocorticosteroids, and in the two cases of membranous glomerulonephritis after treatment with diuretics and/or lisinopril.[28,30]

Clinical manifestations of nephropathy may include hematuria and/or proteinuria and elevation in serum creatinine. Serum creatinine levels and urinalysis with cell counts should be obtained prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion (Table 4). The observation of unexplained hematuria and/or proteinuria or clinically significant changes from baseline in serum creatinine should prompt urgent evaluation for possible nephropathy, since untreated anti-GBM can rapidly progress to renal failure. Observation of isolated proteinuria should prompt further evaluation for other types of nephropathy.

A recently published single-center observational study of 87 patients followed for a mean of seven years did not show any additional safety signals.[32]

Further research is required to find a predictive biomarker that would reliably find patients at risk to develop a secondary autoimmune disease. Earlier evidence that interleukin-21 could serve as such a marker have not been substantiated.[33] A search for immune signatures and/or genetic factors with predictive properties should continue.

As with all drugs that affect the immune system, some rare but potentially serious risks such as opportunistic infections or malignancies may emerge or their dimension may become apparent only after exposure of a larger number of patients to the drug following market approval. The example of progressive multifocal leukoencephalopathy following natalizumab treatment has been informative.[34]

Apparently, absolute lymphocyte counts do not reliably indicate treatment response as shown in a recent study in a cohort of 106 patients who were followed for a median of 99 months.[32] A total of 52% of alemtuzumab-treated (at least two cycles) patients relapsed at some point. Recovery of CD4, CD8 and CD19 cell populations was not different in patients with or without disease activity or accumulation of disability. This emphasizes the need for continued research into the nature and dynamics of the restoration of the immune system and overall immunocompetence.[35]

An open clinical issue needs to be addressed: How many cycles of alemtuzumab can be safely administered and what would trigger repeat infusions? In the most recent account of the Cambridge, United Kingdom (UK) cohort followed for up to 144 months, relapses prompted re-treatment to a total of three cycles in 36%, four cycles in 8% and five cycles in 1% of the 87 patients studied.[32]

Given its mode of action, which appears to effectively re-configure a disturbed immune system, it would also be interesting to assess its potential and safety as induction therapy.

Conclusions

Alemtuzumab is a recent addition to the therapeutic arsenal for relapsing–remitting disease. It has consistently been shown to provide superior efficacy when compared with the baseline disease-modifying agent IFNβ-1a.

Unlike other labeling classifications of RRMS such as "highly active" or "rapidly evolving severe," which require the presence of both clinical *and* imaging features with very specific criteria in each category, active RRMS in the alemtuzumab EU Summary of Product Characteristics (SmPC) is defined based on either clinical or imaging features.[11] This provides the treating neurologist the freedom to select appropriate patients for treatment based on clinical assessment of an individual patient and whether a patient has the ability to comply with monitoring requirements. Long-term monthly monitoring through 48 months after the last alemtuzumab infusion poses a challenge to patient adherence and requires appropriate education both of physicians and patients.

It needs to be determined if and when after the first two or three annual cycles alemtuzumab treatment should be repeated with recrudescence of disease activity.

As with any other newly developed agents, in particular those that exert a powerful impact on the immune system, a thorough assessment of benefits and risks, adherence to long-term monitoring requirements and pharmacovigilance are all mandatory. Alemtuzumab represents a new option for the treatment of active RRMS.

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Conflicts of interest

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References

1. Nylander A and Hafler DA. Multiple sclerosis. *J Clin Invest* 2012; 122: 1180–1188.
2. Hauser SL, Chan JR and Oksenberg JR. Multiple sclerosis: Prospects and promise. *Ann Neurol* 2013; 74: 317–327.
3. Hu Y, Turner MJ, Shields J, et al. Investigation of the mechanism of action of alemtuzumab in a human CD52 transgenic mouse model. *Immunology* 2009; 128: 260–270.
4. Krumbholz M, Derfuss T, Hohlfeld R, et al. B cells and antibodies in multiple sclerosis pathogenesis and therapy. *Nat Rev Neurol* 2012; 8: 613–623.
5. Havari E, Turner MJ, Campos-Rivera J, et al. Impact of alemtuzumab treatment on the survival and function of human regulatory T cells in vitro. *Immunology* 2013; 141: 123–131.
6. Cox AL, Thompson SA, Jones JL, et al. Lymphocyte homeostasis following therapeutic lymphocyte depletion in multiple sclerosis. *Eur J Immunol* 2005; 35: 3332–3342.
7. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing–remitting multiple sclerosis: A randomised controlled phase 3 trial. *Lancet* 2012; 380: 1819–1828.
8. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: A randomised controlled phase 3 trial. *Lancet* 2012; 380: 1829–1839.
9. Genzyme Therapeutics Ltd. Lemtrada™ (alemtuzumab 12 mg concentrate for solution for infusion). EU summary of product characteristics, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003718/WC500150521.pdf (2013, accessed 20 January 2014).
10. CAMMS Trial Investigators, Coles AJ, Compston DA, et al.Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008; 359: 1786–1801.
11. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 clinical trial. *Neurology* 2012; 78: 1069–1078.
12. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet* 1998; 352: 1498–1504.
13. Hartung HP and Aktas O. Evolution of multiple sclerosis treatment: Next generation therapies meet

next generation efficacy criteria. *Lancet Neurol* 2011; 10: 293–295.

14. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab versus interferon beta-1a in early relapsing–remitting multiple sclerosis: Post-hoc and subset analyses of clinical efficacy outcomes. *Lancet Neurol* 2011; 10: 338–348.
15. Freedman MS, Kaplan JM and Markovic-Plese S. Insights into the mechanisms of the therapeutic efficacy of alemtuzumab in multiple sclerosis. *J Clin Cell Immunol* 2013; 4: 1000152.
16. Turner MJ, LaMorte MJ, Chretien N, et al. Immune status following alemtuzumab treatment in human CD52 transgenic mice. *J Neuroimmunol* 2013; 261: 29–36.
17. Rao SP, Sancho J, Campos-Rivera J, et al. Human peripheral blood mononuclear cells exhibit heterogeneous CD52 expression levels and show differential sensitivity to alemtuzumab mediated cytolysis. *PLoS One* 2012; 7: e39416.
18. Jones JL, Anderson JM, Phuah CL, et al. Improvement in disability after alemtuzumab treatment of multiple sclerosis is associated with neuroprotective autoimmunity. *Brain* 2010; 133: 2232–2247.
19. Zhang X, Tao Y, Chopra M, et al. Differential reconstitution of T cell subsets following immunodepleting treatment with alemtuzumab (anti-human CD52 monoclonal antibody) in patients with relapsing–remitting multiple sclerosis. *J Immunol* 2013; 191: 5867–5874.
20. Kovarova I, Arnold DL, Cohen J, et al. Alemtuzumab pharmacokinetics and pharmacodynamics in Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS I). European Neurological Society 22nd Meeting, 9–12 June 2012, Prague, Czech Republic, Poster P341.
21. Fernandez O, Arnold DL, Cohen J, et al. Alemtuzumab improves disability by month 6 independent of relapse history in relapsing–remitting multiple sclerosis patients: CARE-MS II. European Neurological Society 23rd Meeting, 8–11 June 2013, Barcelona, Spain.
22. McCarthy CL, Tuohy O, Compston DAS, et al. Immune competence after alemtuzumab treatment of multiple sclerosis. *Neurology* 2013; 81: 872–876.
23. Wray S, Arnold DL, Johen J, et al. Herpes infection risk reduced with acyclovir prophylaxis after alemtuzumab. Consortium of Multiple Sclerosis Centers 2013 Annual Meeting, 29 May–1 June 2013, Orlando, FL, USA, Poster DX60.
24. Jones JL, Thompson SA, Loh P, et al. Human autoimmunity after lymphocyte depletion is caused by homeostatic T-cell proliferation. *Proc Natl Acad Sci U S A* 2013; 110: 20200–20205.
25. Krupica T, Fry TJ and Mackall CL. Autoimmunity during lymphopenia: A two-hit model. *Clin Immunol* 2006; 120: 121–128.
26. Daniels GH, Vladic A, Brinar V, et al. Alemtuzumab-related thyroid dysfunction in a phase 2 trial of patients with relapsing–remitting multiple sclerosis. *J Clin Endocrinol Metab* 2013; 99: 80–89.
27. Miller T. Detection, incidence, and management of thyroid autoimmunity in Comparison of Alemtuzumab and Rebif in Multiple Sclerosis (CARE-MS) I and II. 65th Annual Meeting of the American Academy of Neurology (AAN). 16–23 March 2013, San Diego, CA, USA, P01.173.
28. Cuker A, Coles AJ, Sullivan H, et al. A distinctive form of immune thrombocytopenia in a phase 2 study of alemtuzumab for the treatment of relapsing–remitting multiple sclerosis. *Blood* 2011; 118: 6299–6305.
29. Clatworthy MR, Wallin EF and Jayne DR. Anti-glomerular basement membrane disease after alemtuzumab. *N Engl J Med* 2008; 359: 768–769.
30. Wynn D, Arnold DL, Cohen JA, et al. Detection, incidence, and management of glomerulonephritis in the alemtuzuamb clinical development program. European Committee for Treatment & Research in Multiple Sclerosis 29th Congress, 2–5 October 2013, Copenhagen, Denmark Poster P597.
31. Meyer D, Coles A, Oyuela P, et al. Case report of anti-glomerular basement membrane disease following alemtuzumab treatment of relapsing–remitting multiple sclerosis. *Mult Scler Relat Disord* 2013; 2: 60–63.
32. Tuohy O, Costelloe L, Hill-Cawthorne G, et al. Alemtuzumab treatment of multiple sclerosis: Long-term safety and efficacy. *J Neurol Neurosurg Psychiatry*. Epub ahead of print 21 May 2014. DOI: 10.1136/jnnp-2014–307721.
33. Azzopardi L, Thompson SAJ, Harding KE, et al. Predicting autoimmunity after alemtuzumab treatment of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2014; 85: 795–798.
34. Clanet MC, Wolinsky JS, Ashton RJ, et al. Risk evaluation and monitoring in multiple sclerosis therapeutics. *Mult Scler*. Epub ahead of print 30 November 2013. 2014; 20: 1306–1311. DOI: 10.1177/1352458513513207.
35. Kousin-Ezewu O, Azzopardi L, Parker RA, et al. Accelerated lymphocyte recovery after alemtuzumab does not predict multiple sclerosis activity. *Neurology* 2014; 82: 2158–2164.