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Original Research Paper

Infection risk with alemtuzumab decreases over time: pooled analysis of 6-year data from the CAMMS223, CARE-MS I, and CARE-MS II studies and the CAMMS03409 extension study

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Abstract

Background: Reduced MS disease activity with alemtuzumab versus subcutaneous interferon beta-1a (SC IFNB-1a) in core phase 2/3 studies was accompanied by increased incidence of infections that were mainly nonserious and responsive to treatment. Alemtuzumab efficacy was durable over 6 years.

Objective: To evaluate infections over 6 years in alemtuzumab-treated patients.

Methods: Three randomized trials (CAMMS223, Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS) I, and CARE-MS II) compared two courses of alemtuzumab 12 mg with SC IFNB-1a 44 μg in patients with active relapsing-remitting MS. An extension study (CAMMS03409) provided further evaluation and as-needed alemtuzumab retreatment.

Results: Infections occurred more frequently with alemtuzumab 12 mg than SC IFNB-1a during Years 1 (58.7% vs 41.3%) and 2 (52.6% vs 37.7%), but declined for alemtuzumab-treated patients in Years 3 (46.6%), 4 (42.8%), 5 (40.9%), and 6 (38.1%). Serious infections were uncommon (1.0%–1.9% per year). Infections were predominantly (>95%) mild to moderate and included upper respiratory tract infections, urinary tract infections, and mucocutaneous herpetic infections. Prophylactic acyclovir reduced herpetic infections. Lymphocyte counts after alemtuzumab therapy did not predict infection risk.

Conclusion: Infections with alemtuzumab were mostly mild to moderate and decreased over time, consistent with preservation of components of protective immunity.

Keywords: Alemtuzumab, disease-modifying therapy, infection, relapsing-remitting multiple sclerosis, safety

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Introduction

Alemtuzumab (LEMTRADA®; Sanofi, Cambridge, MA) is a humanized monoclonal antibody approved in >70 countries for treatment of relapsing-remitting multiple sclerosis (RRMS).[1,2] It is given as infusions of 12 mg/day on five consecutive days at baseline and on three consecutive days 12 months later, with up to two additional treatment courses (three consecutive days) in patients with MS disease activity.[1–4] In phase 2 and 3 clinical trials, alemtuzumab had superior efficacy over 24–36 months versus subcutaneous interferon beta-1a (SC IFNB-1a; Rebif®) given three times per week.[5–7] Relapses were significantly decreased with alemtuzumab versus SC IFNB-1a in each study, and the risk of confirmed disability worsening was significantly reduced with alemtuzumab in the phase 2 CAMMS223 trial and in the phase 3 Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS) II trial.[5,7] Alemtuzumab also reduced magnetic resonance imaging (MRI) lesion activity and brain volume loss.[6,7] Efficacy was durable over 6 years in the absence of

continuous treatment in the CAMMS03409 extension study.[8–10] Durable efficacy and a well-characterized, manageable safety profile give alemtuzumab a positive benefit:risk profile.

Alemtuzumab selectively targets cell surface CD52 to deplete circulating T and B cells,[11] leading to a distinctive pattern of cellular repopulation.[12] T cells repopulate steadily after each treatment course, but generally do not return to baseline by 12 months post treatment.[13] B cell counts return to baseline or above 3–6 months post treatment.[13] Proportions of lymphocyte subsets are altered following alemtuzumab treatment, including a relative increase in regulatory and memory T cells within the overall T cell population.[12] The suppressive function of T regulatory cells may be restored, and the cytokine profile shifts from proinflammatory to anti-inflammatory.[14,15] Alemtuzumab minimally depletes subsets of innate immune cells due to their lower expression of cell surface CD52.[13,16] Immunoregulatory natural killer cell subsets may undergo a relative expansion after alemtuzumab treatment, persisting for 24 months.[17,18] Serum immunoglobulin concentration and tissue-resident effector memory T cells are unaffected.[19,20]

In the phase 2 and 3 studies, overall infection incidence ranged from 66% to 77% with alemtuzumab 12 mg versus 45% to 66% with SC IFNB-1a.[5–7] Most were not serious; the incidence of serious infections was 2%–4% with alemtuzumab 12 mg and 1%–2% with SC IFNB-1a.[5–7] The modestly elevated infection incidence suggests that, despite immunosuppression, important components of innate and adaptive immunity are left intact. Here, we use pooled 6-year data from phase 2 and 3 and extension studies to characterize infections in alemtuzumab-treated patients over the longer term and discuss possible mechanisms by which alemtuzumab suppresses MS disease processes while apparently preserving components of protective immunity.

Patients and methods

Core study methods are described fully elsewhere.[5–7] Patients in the phase 2 (CAMMS223; ClinicalTrials.gov identifier NCT00050778) and phase 3 (CARE-MS I, NCT00530348; and CARE-MS II, NCT00548405) studies had active disease and were randomized to receive either alemtuzumab or SC IFNB-1a (Figure 1). Alemtuzumab 12 mg or 24 mg was administered by intravenous (IV) infusion on five consecutive days at the start of treatment and on three consecutive days 12 months later (the 24-mg dose was not available in CARE-MS I). A third course (optional; per investigator's discretion) consisting of infusions on three consecutive days at Month 24 was given to 21% of patients in the core CAMMS223 study. SC IFNB-1a 44 μg was administered three times per week. Participants in each study could enroll in the extension study (CAMMS03409; NCT00930553) for further follow-up and as-needed alemtuzumab retreatment for clinical or radiologic activity (12 mg/day infusion on three consecutive days at least 12 months after the most recent course).[8,9] Patients provided written informed consent at core study enrollment and before entering the extension study.

During the phase 3 studies, a protocol amendment introduced a requirement for herpes prophylaxis using acyclovir (200 mg by mouth twice daily) in alemtuzumab-treated patients, beginning on the first day of each alemtuzumab treatment course and continuing for 28 days after completion. No other infection prophylaxis was routinely provided.

The pooled data presented here represent a total 6-year follow-up of patients in the alemtuzumab 12-mg arm of CARE-MS I and II, CAMMS223 (and its extended follow-up period),[21] and the CAMMS03409 extension study. Data on SC IFNB-la-treated patients are presented for Years 1 and 2 only, as there was no SC IFNB-1a arm in the extension study. All patients with RRMS who received alemtuzumab 12 mg or SC IFNB-1a in the core studies were included. Several notable opportunistic infections that occurred in the alemtuzumab 24-mg arms are also discussed.

Serious infections were defined according to the World Health Organization: either life-threatening; requiring or prolonging inpatient hospitalization; causing persistent or significant disability/incapacity, congenital anomaly, or death; or requiring medical/surgical intervention to prevent these outcomes. Because of the timing of the introduction of acyclovir, its use during Course 3 and subsequent courses was limited to the CARE-MS extension population and one patient in CAMMS223, not a representative pooled population. Therefore, no analysis of infections in relation to acyclovir use following administration of Course 3 was carried out. Results are reported as incidences (percentage of patients with $\geq$1 event). Incidence rates adjusted for follow-up time are also appropriate to report in trials with long-term follow-up.[22] Therefore, exposure-adjusted incidence rates (EAIRs) per 100 patient-years ([number of patients with specific event divided by total annual exposure time among patients at risk of initial occurrence of event] $\times$ 100) are reported in time intervals. EAIRs by treatment course

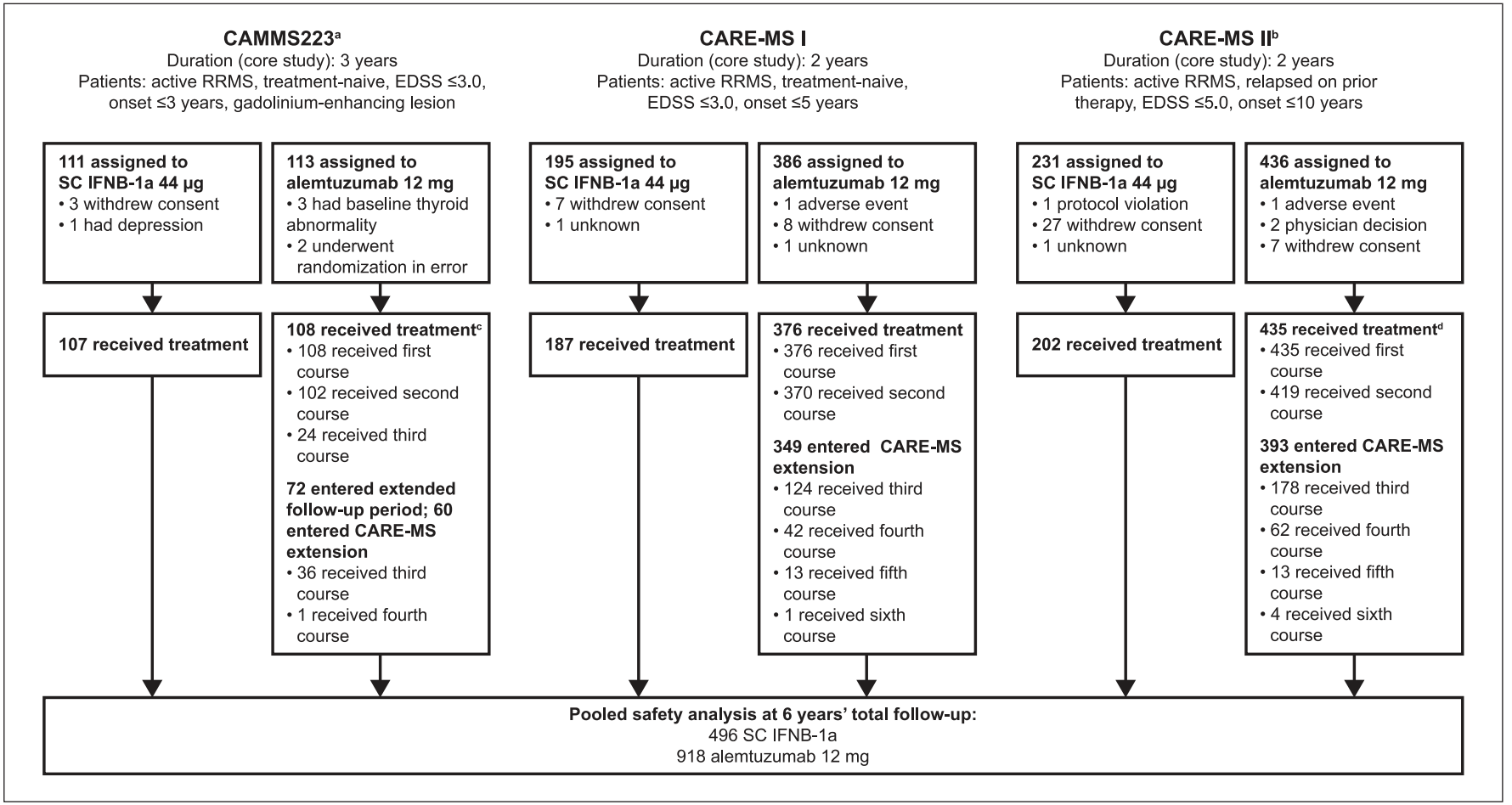

Figure 1. CONSORT diagram of patients included in safety analysis.
CARE-MS: Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis; EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SC IFNB-1a: subcutaneous interferon beta-1a.
[a]The 24-mg treatment arm is not shown ($n = 108$ received treatment).
[b]The 24-mg treatment arm is not shown ($n = 170$ received treatment).
[c]One patient was excluded from analysis due to misdiagnosis.
[d]Nine patients randomized to alemtuzumab 24 mg actually received the 12-mg dose.

Table 1. Baseline characteristics of pooled population.

Characteristic	SC IFNB-1a 44 µg (n=496)	Alemtuzumab 12 mg (n=918)
Age, years	34.2 (8.78)	33.8 (8.23)
Female, *n* (%)	323 (65.1)	599 (65.3)
Time since initial relapse, years	3.0 (2.50)	3.1 (2.42)
Number of relapses in years before randomization	1.7 (0.80)	1.7 (0.84)

SC IFNB-1a: subcutaneous interferon beta-1a.
Values shown are mean (standard deviation), unless otherwise stated.

were calculated from the start of one course until the start of the next course. If no other course was given, the time frame was until the end of follow-up for the 6-year period. EAIRs by month were calculated per 100 patient-months. Opportunistic infections were identified based on medical review of each patient with infection, taking into account the pathogen, temporal association with alemtuzumab treatment, medical history, and concomitant medications. Lymphocyte subset counts temporally related to the occurrence of treatment-emergent infections were evaluated using available data from the CARE-MS studies and CAMMS03409. For each post-baseline time point, infections were counted if they had onset within the specific time window of that time point. For patients who received retreatment, data up to Course 3 onset date were included.

Results

Patient disposition

A total of 1414 patients with RRMS were analyzed (alemtuzumab 12 mg: n=918; SC IFNB-1a: n=496; Figure 1). Most patients (97.4%) treated with alemtuzumab 12 mg received at least two courses; 37.8%, 11.5%, and 2.8% received at least a third, fourth, and/or a fifth course, respectively. Baseline characteristics are presented in Table 1.

Overview of infections

Pooled results from the 6-year follow-up showed that infections were common across treatment groups, but more frequent with alemtuzumab 12 mg than with SC IFNB-1a (Table 2). The increased infection incidence with alemtuzumab was apparent at every monthly time point, but was most marked in the first month after the first course of treatment (Figure 2(a)). No corresponding increase was seen after the second course of alemtuzumab treatment at Month 13, which may be due, in part, to more patients receiving prophylactic acyclovir with the second course. In alemtuzumab-treated patients, infection incidence by month was lower in Years 3–6 compared with Years 0–2. Infection EAIR was relatively stable with each successive alemtuzumab treatment course (Figure 2(b)).

The majority of infections were mild to moderate in severity (i.e. Grades 1 or 2 using the Common Terminology Criteria for Adverse Events; Table 2) and were most commonly upper respiratory tract infections including nasopharyngitis and sinusitis, urinary tract infections, and mucocutaneous herpes simplex infections (Table 3). One fatal infection occurred in the alemtuzumab arm (sepsis in Year 3; previously reported).[6] No infection led to study discontinuation, although one led to treatment withdrawal (HIV infection).

Serious infection incidences were higher with alemtuzumab 12 mg than with SC IFNB-1a (1.9% vs 0.4%; Supplementary Table 1) during the first year of follow-up, but were stable in the alemtuzumab 12-mg group in Years 2 (1.0%), 3 (1.5%), 4 (1.6%), 5 (1.3%), and 6 (1.0%). The most common serious infections (occurring in more than one patient) were pneumonia, varicella zoster, appendicitis, gastroenteritis, and sepsis.

Incidences of infections and serious infections were similar between the overall study population and patients who received only the initial two courses of alemtuzumab 12 mg at Months 0 and 12, and no further treatment through Year 6 (Supplementary Table 2).

Herpetic infections and acyclovir prophylaxis

Acyclovir prophylaxis was introduced after initiation of the phase 3 studies. Herpes infections were increased with alemtuzumab 12 mg versus SC IFNB-1a during Years 1 (11.1% vs 1.8%) and 2 (7.7% vs 1.3%). Herpes simplex infections with alemtuzumab were

Table 2. Overview of infections and serious infections.

	SC IFNB-1a 44 µg		Alemtuzumab 12 mg						
	Year 1 (*n*=496)	Year 2 (*n*=459)	Year 1 (*n*=918)	Year 2 (*n*=917)	Year 3 (*n*=875)	Year 4 (*n*=824)	Year 5 (*n*=787)	Year 6 (*n*=766)	EAIR per 100 patient-years Years 0–6
Any infection, *n* (%)	205 (41.3)	173 (37.7)	539 (58.7)	482 (52.6)	408 (46.6)	353 (42.8)	322 (40.9)	292 (38.1)	50.85
Grade 1	100 (20.2)	78 (17.0)	282 (30.7)	260 (28.4)	185 (21.1)	170 (20.6)	155 (19.7)	125 (16.3)	19.68
Grade 2	147 (29.6)	118 (25.7)	403 (43.9)	348 (37.9)	295 (33.7)	262 (31.8)	227 (28.8)	215 (28.1)	32.34
Grade 3	2 (0.4)	4 (0.9)	17 (1.9)	13 (1.4)	11 (1.3)	9 (1.1)	8 (1.0)	9 (1.2)	1.25
Grade 4	0	0	0	1 (0.1)	0	2 (0.2)	0	0	0.06
Grade 5	0	0	0	0	1 (0.1)	0	0	0	0.02
Leading to study discontinuation	0	0	0	0	0	0	0	0	0
Leading to treatment withdrawal	0	0	0	0	0	0	1 (0.1)	0	0.02
Any serious infection, *n* (%)	2 (0.4)	3 (0.7)	17 (1.9)	9 (1.0)	13 (1.5)	13 (1.6)	10 (1.3)	8 (1.0)	1.26

SC IFNB-1a: subcutaneous interferon beta-1a; EAIR: exposure-adjusted incidence rate per 100 patient-years, calculated as (number of patients with a specific event divided by total exposure time among patients at risk of an initial occurrence of the event) × 100.
Percentage is based on the number of patients having an adverse event in the reported year divided by the total number of patients followed up in that year.

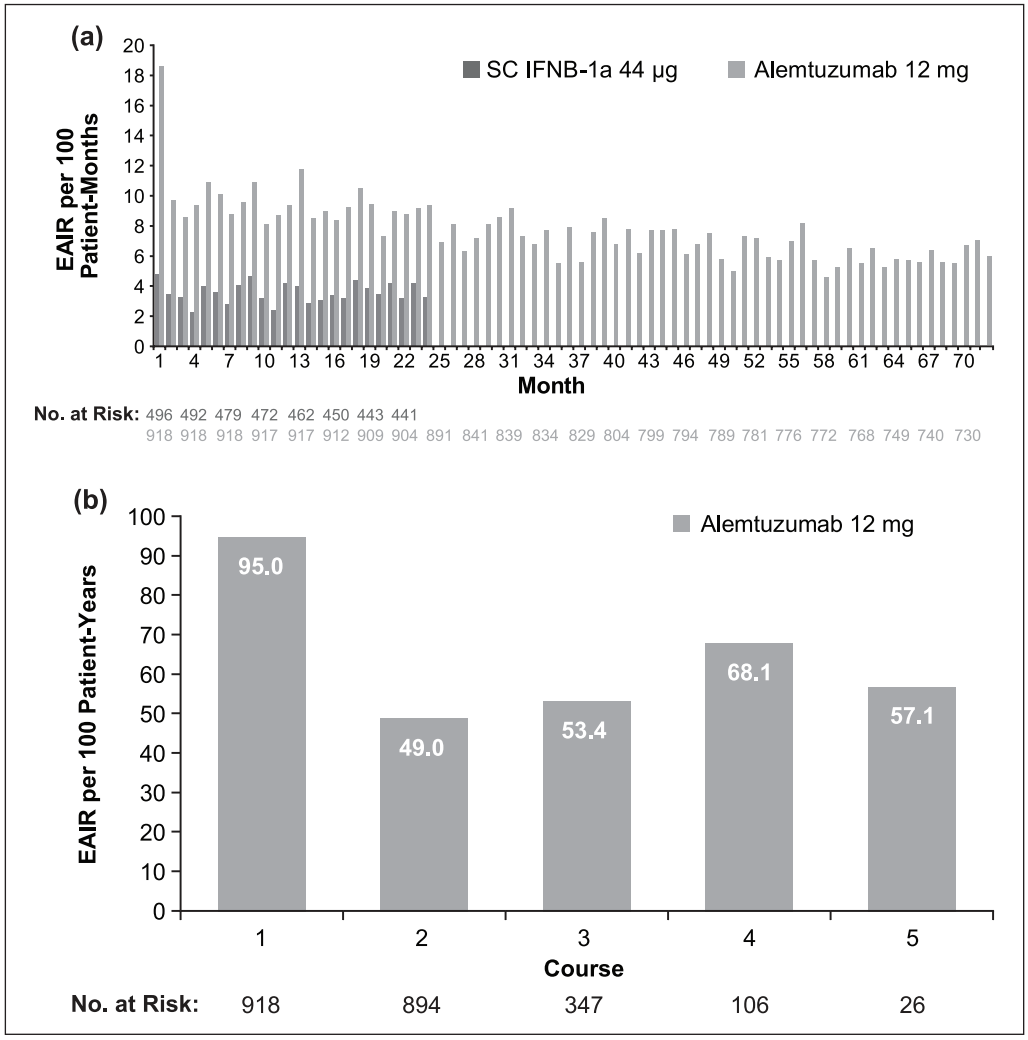

Figure 2. Incidence and rate of treatment-emergent infections. EAIR of treatment-emergent infections by month (a) and by treatment course (b). Alemtuzumab data for Months 0–72 are pooled from CAMMS223 (and its extended follow-up period), CARE-MS I, and CARE-MS II core studies and the extension study. SC IFNB-1a data are pooled from the three core studies for Months 0–24.
CARE-MS: Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis; EAIR: exposure-adjusted incidence rate; SC IFNB-1a: subcutaneous interferon beta-1a.

predominantly mucocutaneous and declined after the second year (for Years 1–6, respectively: 8.6%, 5.2%, 2.7%, 2.2%, 1.9%, and 2.9%); this pattern is likely related to the lower proportion of patients receiving alemtuzumab treatment in Years 3–6 and an increased rate of herpes prophylaxis in those years. Incidence of herpes zoster was stable in each year (for Years 1–6, respectively: 2.0%, 2.4%, 3.1%, 1.9%, 2.4%, and 2.6%). Other herpetic infections reported included varicella ($n=8$ patients) and herpes meningitis ($n=1$). Acyclovir prophylaxis markedly reduced herpes simplex incidence in the first month after each treatment course (Course 1, 4.9% without prophylaxis vs 0.5% with prophylaxis; Course 2, 2.4% vs 0.8%, respectively).

There were eight serious events of varicella zoster over the 6-year follow-up period in patients who received alemtuzumab 12 mg. One case was multidermatomal varicella zoster. One case of varicella zoster meningitis (Grade 3) was observed in Month 6, diagnosed by polymerase chain reaction testing of the cerebrospinal fluid. The infection resolved in 2 weeks on treatment with IV acyclovir, and the patient received the second course of alemtuzumab treatment without recurrence.

Opportunistic infections

Infections deemed opportunistic were reported in seven patients (0.8%) over the 6-year follow-up and

Table 3. Incidence of the most common infections (incidence > 5% in either group per year).

Incidence, *n* (%)	SC IFNB-1a 44 µg		Alemtuzumab 12 mg						
	Year 1 (*n* = 496)	Year 2 (*n* = 459)	Year 1 (*n* = 918)	Year 2 (*n* = 917)	Year 3 (*n* = 875)	Year 4 (*n* = 824)	Year 5 (*n* = 787)	Year 6 (*n* = 766)	EAIR per 100 patient-years Years 0–6
Nasopharyngitis	58 (11.7)	47 (10.2)	146 (15.9)	124 (13.5)	108 (12.3)	91 (11.0)	85 (10.8)	85 (11.1)	8.5
Urinary tract infection	25 (5.0)	22 (4.8)	109 (11.9)	91 (9.9)	95 (10.9)	87 (10.6)	80 (10.2)	71 (9.3)	6.9
Upper respiratory tract infection	39 (7.9)	34 (7.4)	102 (11.1)	88 (9.6)	74 (8.5)	66 (8.0)	48 (6.1)	48 (6.3)	6.2
Sinusitis	25 (5.0)	13 (2.8)	64 (7.0)	55 (6.0)	47 (5.4)	50 (6.1)	36 (4.6)	30 (3.9)	4.0
Herpes simplex[a]	6 (1.2)	4 (0.9)	79 (8.6)	48 (5.2)	24 (2.7)	18 (2.2)	15 (1.9)	22 (2.9)	2.9

SC IFNB-1a: subcutaneous interferon beta-1a; EAIR: exposure-adjusted incidence rate per 100 patient-years, calculated as (number of patients with a specific event divided by total exposure time among patients at risk of an initial occurrence of the event) × 100.
Percentage is based on the number of patients having an adverse event in the reported year divided by the total number of patients followed up in that year.
[a]Includes preferred terms "herpes simplex," "oral herpes," "genital herpes," and "herpes simplex ophthalmic."

included herpes infections ($n = 3$; varicella zoster meningitis, varicella zoster, and multidermatomal varicella zoster; described previously), candidiasis ($n = 4$), cytomegalovirus infection ($n = 1$), and acute disseminated tuberculosis ($n = 1$). Two patients had both herpes and *Candida* infections. Three opportunistic infections were serious (varicella zoster meningitis, acute disseminated tuberculosis, and esophageal candidiasis). One patient (0.2%) in the SC IFNB-1a group developed an opportunistic infection (renal tuberculosis) during the core studies.

One case of active tuberculosis occurred with alemtuzumab 12 mg. Acute disseminated tuberculosis of both lungs (Grade 3; no extrapulmonary disease) occurred after two courses of alemtuzumab 12 mg. The case was from a region of known endemic infection and resolved with conventional antituberculosis treatment.[6]

Shortly after the second course of treatment, a patient receiving alemtuzumab 12 mg developed Grade 3 esophageal candidiasis accompanied by gastritis and abdominal pain. The patient was treated with fluconazole and nystatin for candidiasis and also received antibiotics for management of preexisting diverticular disease. The patient received a second course of alemtuzumab, using nystatin prophylaxis for 1 month after treatment; no recurrence of candidiasis occurred.

Several notable opportunistic infections occurred in patients who received the 24-mg dose of alemtuzumab. Grade 2 *Listeria* meningitis occurred 12 days after completing Course 1 in a patient who had recently eaten unpasteurized cheese. The patient responded to treatment with amoxicillin and gentamicin, and received a second course of alemtuzumab, without recurrence of listeriosis. Patients are now advised to avoid undercooked meats or unpasteurized dairy products for 2 weeks prior to, during, and at least 1 month after alemtuzumab infusion. Second, a nonserious case of Grade 2 cytomegalovirus infection leading to a mononucleosis-like syndrome developed 12 days after a patient received the first dose of alemtuzumab 24 mg and was diagnosed by polymerase chain reaction. The infection resolved 1 month later with no end-organ involvement, after treatment with acetaminophen, valganciclovir, and sulfamethoxazole/trimethoprim. The patient continued in the study and received a second course of alemtuzumab. Screening for cytomegalovirus was not routinely performed during the trials.

Other serious infections

Serious pneumonia was reported in 11 patients who received alemtuzumab 12 mg, with 4 patients in Year 2

(1 patient had a recurrence of pneumonia), 1 patient in Year 3, 5 patients in Year 4, and 1 patient in Year 6. Severity was reported as Grade 2 ($n=5$), 3 ($n=5$), or 4 ($n=1$). Three cases occurred in patients who were current smokers, of which all occurred in Year 4. All cases of serious pneumonia responded to antibiotic treatment and resolved within 1 month of onset.

Sepsis was documented in five patients treated with alemtuzumab 12 mg. In CAMMS223, a patient received a single course of alemtuzumab and subsequently received mitoxantrone and then cyclophosphamide for treatment of refractory MS. At 24 months post alemtuzumab treatment, during treatment with cyclophosphamide, the patient developed neutropenia and sepsis, which responded to treatment with broad-spectrum antibiotics and filgrastim. Two cases of sepsis associated with pancytopenia also occurred in the CAMMS03409 extension study, one of which was fatal. The fatal case had onset approximately 18 months after the second course of alemtuzumab. The patient developed Grade 4 autoimmune pancytopenia, was hospitalized 1 week later, treated with filgrastim, corticosteroids, and IV immunoglobulin, and the patient's cell counts normalized. He was discharged after 5 weeks. Thereafter, the patient did not continue corticosteroid therapy as prescribed, and 8 days later developed recurrence of pancytopenia with fever, mucocutaneous bleeding, and sepsis, from which he died.[6] The other sepsis case associated with pancytopenia occurred 16 months after the last alemtuzumab dose in a patient who had previously developed immune thrombocytopenia and autoimmune hemolytic anemia, from which the patient had recovered. He was diagnosed with Grade 3 sepsis and pancytopenia, hospitalized, and treated with broad-spectrum antibiotics and corticosteroids. He recovered 9 days later, with no recurrence of sepsis or pancytopenia. Two additional cases of sepsis occurred in CAMMS03409 (Years 4 and 5). In the first, the patient developed Grade 4 sepsis with neutropenia, 25 months after the second course of alemtuzumab. The patient was treated with filgrastim, ceftriaxone, metronidazole, vancomycin, and piperacillin/tazobactam, and recovered. In the second case, the patient developed Grade 3 sepsis 28 months after the third course of alemtuzumab and recovered after treatment with meropenem, cephalexin, and ciprofloxacin.

Infections and lymphocyte subset counts

Lymphocyte analysis showed that alemtuzumab depleted circulating T and B cells, with nadir lymphocyte counts at the earliest post-treatment time point (Month 1).[7,13] Innate immune cell counts (monocytes, neutrophils, eosinophils, and basophils) showed minimal or transient depletion.[7,13] Regardless of whether patients developed an infection within the lymphocyte sampling window, their absolute counts of $CD4^+$ T cell, $CD8^+$ T cell, and $CD19^+$ B cell subsets were similar at all the time points examined (Figure 3). Furthermore, lymphocyte counts before an alemtuzumab treatment course did not predict subsequent infection risk.

Discussion

The highly effective reduction in MS disease activity observed with alemtuzumab compared with SC IFNB-1a is accompanied by an increased incidence of infections that are typically nonserious and that respond to conventional therapies.[5–7] This pooled 6-year analysis across the alemtuzumab clinical development program for RRMS demonstrated that infections were infrequently severe or serious, and infection risk peaked after the first course of alemtuzumab and then declined over time. Serious infections were uncommon. Herpes simplex infections were most frequent in the first month following each alemtuzumab treatment course and were reduced by acyclovir. In addition to acyclovir, product labeling recommends other measures to prevent or manage infections after alemtuzumab treatment, including screening for hepatitis B and C viruses, human papilloma virus, and tuberculosis infection; delaying treatment in patients with severe active infection; and vaccinating against varicella zoster virus (Table 4).[1,2] Patients should also avoid potential sources of foodborne *Listeria* for at least 2 weeks before and 1 month after alemtuzumab infusion[2]; however, guidance also exists for treating patients with prophylactic co-trimoxazole for 1 month after alemtuzumab treatment.[23] In postmarketing surveillance reporting, *Listeria monocytogenes* was the most common opportunistic infection (0.26%), followed by cytomegalovirus infection (0.13%).[24]

The risk of infection is only modestly elevated with alemtuzumab treatment, contributing to the overall positive benefit:risk profile of the drug. The alemtuzumab magnitude of therapeutic effect on relapse, disability improvement, and preservation of brain volume puts it into the category of high-efficacy agents, and these effects are durable over 6 years. In contrast to other high-efficacy agents,[25,26] no cases of progressive multifocal leukoencephalopathy have been attributed to alemtuzumab, either in clinical trials or in postmarketing surveillance.[24]

Considering the low blood lymphocyte counts observed acutely after alemtuzumab treatment and the time course for recovery of T cell counts, it may be

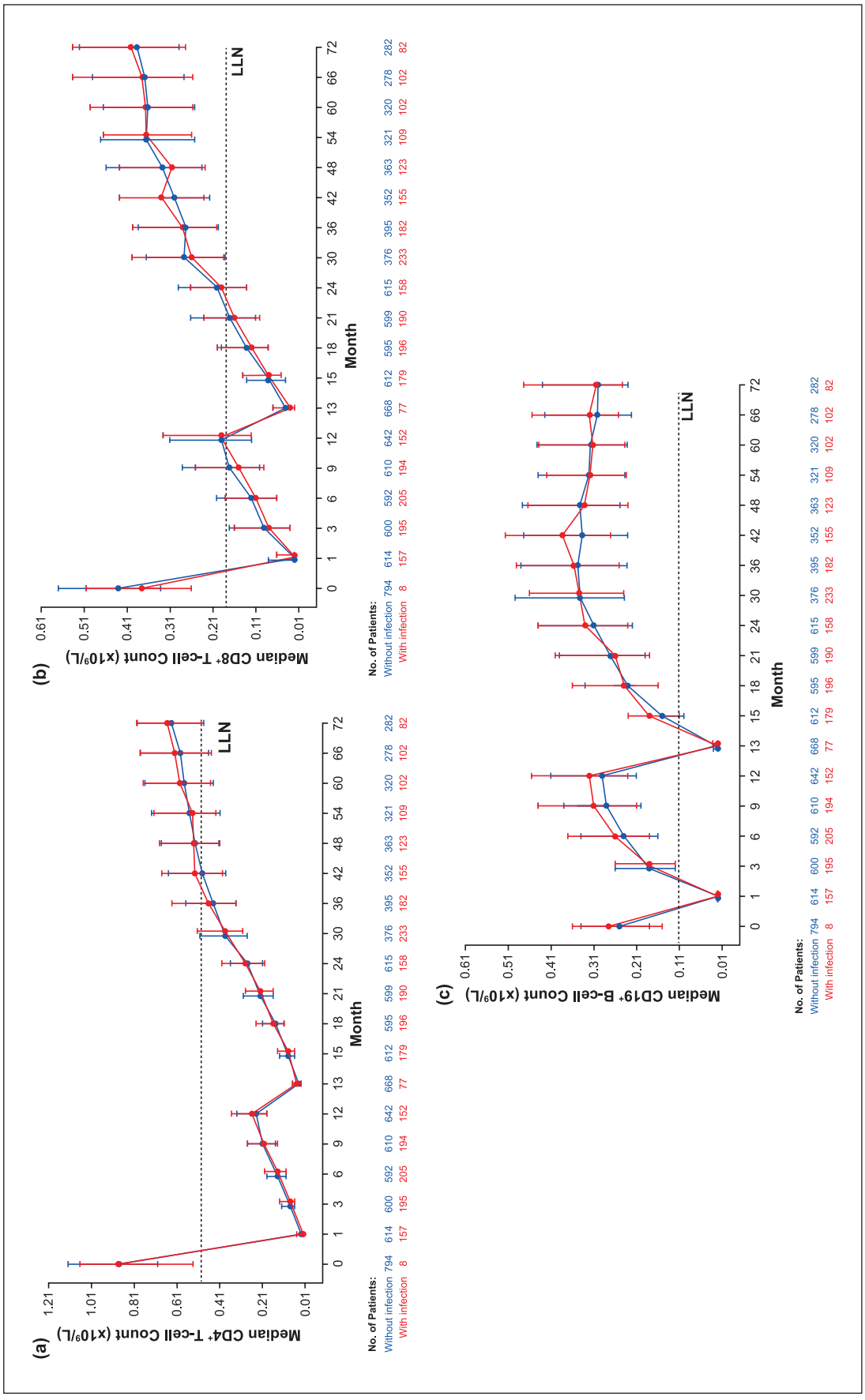

Figure 3. Median lymphocyte subset counts by the occurrence of treatment-emergent infections over time. For each post-baseline time point, infections were counted if they had onset within the specific time window of that time point. For patients who received retreatment, data up to Course 3 onset date were included. $CD4^+$ T cells (a), $CD8^+$ T cells (b), and $CD19^+$ B cells (c). Error bars denote the first and third quartiles.
LLN: lower limit of normal.

Table 4. Summary of key infection concerns and prevention measures.

Infection	Clinical trial incidence over 6 years (12-mg treatment arms)[a]	Time frame of prevention[1,2]	Prevention measures[1,2]
Herpetic infection (any)	25.1%[b]	Starting on the first day of alemtuzumab infusion and continuing for 1 month[2], or for at least 2 months or until the $CD4^+$ lymphocyte count is ⩾200 cells per μL, whichever occurs later[1,c]	Prophylaxis with an oral anti-herpes agent
Herpes zoster	11.9%[b]	6 weeks prior to alemtuzumab initiation	Test for anti-VZV antibodies; consider vaccinating antibody-negative patients
HPV	0	Annually	HPV screening (females)
Tuberculosis	0.1%	Before alemtuzumab initiation	Evaluate all patients for active and inactive tuberculosis before initiation of alemtuzumab; treat tuberculosis-positive patients before initiating alemtuzumab
Listeria	0 (1 case in the 24-mg treatment arm)	2 weeks before and at least 1 month after each alemtuzumab infusion course	Patients should avoid ingestion of uncooked or undercooked meats or unpasteurized dairy products
Hepatitis B and hepatitis C	No data available due to exclusion criteria of studies	Before alemtuzumab initiation	Consider screening patients at high risk for hepatitis B or C before alemtuzumab initiation and exercise caution if administering alemtuzumab to identified carriers, to avoid virus reactivation and irreversible liver damage
General		Before alemtuzumab initiation	Delay treatment with alemtuzumab in patients with severe active infection; consider potential combined effects of alemtuzumab with any other immunosuppressive therapy; do not administer live viral vaccines to patients who have recently received alemtuzumab

VZV: varicella zoster virus; HPV: human papilloma virus.
[a]Incidence rates are given as 6-year cumulative incidence for the pooled phase 2 and phase 3 study populations, and differ from those given in product labeling (2-year incidence rates for pooled phase 3 populations).
[b]Not all patients received herpes prophylaxis with alemtuzumab treatment. Rates of herpes prophylaxis in patients receiving alemtuzumab in Years 1–6 were 46%, 54%, 82%, 89%, 85%, and 83%, respectively.
[c]Product labeling in the European Union recommends herpes prophylaxis for 1 month, consistent with clinical trial procedures. In the United States, product labeling approved by the Food and Drug Administration recommends at least 2 months of anti-herpes treatment, until the $CD4^+$ lymphocyte count reaches ⩾200 cells per μL.

surprising that alemtuzumab did not lead to a marked increase in susceptibility to serious infections. However, these results are consistent with the observation that humoral responses to recall antigens, and vaccination responses to T-dependent and T-independent antigens, were largely normal in patients treated with alemtuzumab 1.5 to 86 months previously.[27]

The relatively modest observed increase in infection incidence with alemtuzumab is likely explained by five aspects of the drug's pharmacodynamic effects. First, certain innate immune cell subsets (e.g. neutrophils, eosinophils, basophils, and natural killer cells) are minimally depleted by alemtuzumab treatment.[11,13] Second, the concentrations of serum immunoglobulins and immunoglobulin G titers to common viruses are unchanged by alemtuzumab treatment,[19,20] probably because long-lived, antibody-secreting plasma cells are CD52-negative.[28] Third, studies have shown that alemtuzumab can lead to differential lymphocyte depletion from blood versus lymphoid organs and tissues.[11,19] Although circulating lymphocytes are efficiently depleted by alemtuzumab, they represent only a minority of the T cell population. Animal studies have shown that T cells in the spleen and lymph nodes are only partially depleted,[11,29] and human studies have demonstrated the presence of tissue-resident effector T cell populations that do not recirculate and are thus resistant to depletion by alemtuzumab.[19] Fourth, experimental models of lymphocyte migration after alemtuzumab suggest preservation of responses to chemotactic stimuli and a retained ability to migrate into inflamed tissue.[30] Finally, the period of maximal T and B cell depletion following alemtuzumab administration is relatively brief; lymphocyte repopulation begins within weeks of treatment, continues throughout the year

before a second treatment course, and resumes within weeks after the second course.[13] Thus, intact innate immunity, pre-formed serum antibodies, relative sparing of noncirculating lymphocytes, preserved trafficking, and repopulation of T and B cells may all potentially contribute to immune competence in alemtuzumab-treated patients. Coupled with high therapeutic efficacy, these data add to the positive benefit:risk profile of alemtuzumab.

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