Accelerated lymphocyte recovery after alemtuzumab does not predict multiple sclerosis activity

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ABSTRACT

Objective: To test the hypothesis that accelerated peripheral blood mononuclear cell recovery after alemtuzumab treatment of multiple sclerosis is associated with recurrent disease activity and to investigate the claim that CD4 counts greater than 388.5×10^6 cells/mL at 12 months can be used to identify patients who may benefit from further treatment.

Methods: A total of 108 patients were followed for a median of 99 months post alemtuzumab. Patients were classified as active or nonactive after each cycle of treatment based on clinical relapse, increasing disability, or new T2/enhancing MRI lesions. These outcomes were correlated with CD4, CD8, CD19, CD56+ NK, and monocyte counts.

Results: Of 108 patients, 56 (52%) relapsed at some point during follow-up. Mean annualized relapse rate after alemtuzumab was 0.17 vs 1.67 prior to treatment (equating to a 90% reduction). Of 108 patients, 28 (26%) met the criteria for sustained accumulation of disability. Median time to the lower limit of normal for CD19, CD8, and CD4 was 3, 19.5, and 32 months, respectively. There was no significant difference in the recovery of any cell population between patients with and without disease activity or accumulation of disability after treatment.

Conclusion: This study does not support the use of cell counts as biomarkers for identifying patients at greater risk of active disease following treatment with alemtuzumab. *Neurology*® 2014;82:2158-2164

GLOSSARY

EDSS = Expanded Disability Status Scale; **IQR** = interquartile range; **LLN** = lower limit of normal; **MS** = multiple sclerosis; **RRMS** = relapsing-remitting multiple sclerosis.

Alemtuzumab has proven efficacy as a treatment for relapsing-remitting multiple sclerosis (MS). In a phase 2 trial, compared with interferon β -1a, alemtuzumab reduced the risk of relapse and sustained accumulation of disability by more than 70% at 3 years, with sustained efficacy at 5 years.^{1,2} Two phase 3 trials (CARE-MS I and CARE-MS II) have confirmed efficacy in treatment-naïve patients and established superiority over interferon β -1a in patients who continue to relapse despite first-line therapy.^{2,3} So alemtuzumab was licensed by the European Medicines Agency⁴ and is entering routine clinical practice in the European Union as a treatment for active MS.

Alemtuzumab is a lymphocyte-depleting anti-CD52 monoclonal antibody. Each cycle causes profound pan-lymphocyte depletion, but the relatively infrequent dosing regimen allows reconstitution to occur. The rate and degree of recovery varies with cell type: B cells recover rapidly, whereas T-cell lymphopenia is prolonged, with CD4 and CD8 cells taking 35 and 20 months, respectively, to reach the lower limit of normal.⁵ During this period of immune reconstitution, 30% of individuals experience thyroid autoimmunity, and 1% develop immune thrombocytopenic purpura; in rare cases, Goodpasture syndrome, autoimmune hemolytic anemia, and autoimmune neutropenia have also been reported.⁶ We have recently shown that the risk of developing autoimmunity after alemtuzumab is unrelated to rate of T-cell reconstitution but rather reflects the degree to which recovery occurs by expansion of cells that have escaped

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Supplemental data
 at Neurology.org

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depletion rather than thymopoiesis.⁷ A recently published report,⁸ however, suggested that peripheral CD4 recovery can be used to predict MS disease activity after treatment, with counts greater than 388.5×10^6 cells/mL at 12 months following therapy identifying patients who are likely to have recurrent disease activity and who may therefore benefit from further treatment. Given the clear clinical implications of this claim, we reassessed this finding in the Cambridge cohort—a larger group of patients in whom the role of alemtuzumab in relapsing-remitting MS was originally evaluated and therefore provides prolonged duration of follow-up.

METHODS Patients and procedures. All patients had relapsing-remitting MS (RRMS) and had participated in CAMMS223 (a phase 2 randomized controlled trial) and CAMMS 224 or SM3 (both investigator-led, open-label studies). CAMMS223 key eligibility criteria were disease onset within 3 years, at least 2 clinical relapses during the previous 2 years, and a score of 3 or less on the Expanded Disability Status Scale (EDSS). Patients were included in CAMMS 224 and SM3 if they had at least one relapse in the previous year, an EDSS score of 6.0 or less, and disease duration of less than 10 years. Subsequently, all patients entered either CAMSAFE (an investigator-led long-term observational study) or the extension phase of the CAMMS223 trial. The first patient from this cohort was treated on November 22, 1999, with the date for final collection of data January 1, 2013.

Standard protocol approvals, registrations, and patient consents. All studies were approved by a regional ethics board and institutional research committee. All patients gave written informed consent.

Clinical treatment and follow-up protocol. All patients received at least 2 elective cycles of alemtuzumab given annually, with the potential for further cycles if there was clinical or radiologic evidence of ongoing disease activity. Patients were reviewed at 1 and 3 months and then quarterly for the first 2 years after each treatment cycle. For the following 2 years, they were seen biannually and then at least annually thereafter. Patients were also seen whenever a relapse was suspected.

Outcome assessments. For participants in the CAMMS223 study, EDSS scores were determined quarterly in a blinded fashion by a neurologist who also adjudicated possible relapses. The same assessor measured the EDSS of patients in the CAMMS224 and SM3 studies, albeit less frequently. Sustained accumulation of disability was defined as an increase of 1.5 EDSS points from a baseline of 0, or an increase of ≥ 1.0 if the baseline was ≥ 1.0 confirmed over 6 months. A relapse was defined as new neurologic symptoms attributable to MS lasting >48 hours with an objective change in neurologic examination. Peripheral blood mononuclear cell phenotyping was performed at baseline and then quarterly for the first 36 months and then at least annually (including total lymphocyte count, CD4, CD8, CD19, CD56-NK, and monocyte counts). Brain MRI scans were performed in most patients with a suspicion of active disease prior to retreatment with alemtuzumab. Monthly MRI scans were performed in a subset of patients from the SM3 study. A number of clinically

inactive patients had interval MRI scans to look for subclinical activity and to provide a means for comparison in case of future disease activity.

Statistical analysis. Median time for recovery to the lower limit of normal (LLN) was calculated for each cell subset. All data were categorized depending on the cycle of alemtuzumab treatment. Patients were placed into “active” or “nonactive” groups independent of when an event took place within a particular treatment cycle. Therefore, within each cycle, patients were defined as being relapse-free or relapsing, disability-free or having accumulated disability, or having reached a positive composite endpoint (defined as having relapsed, or accumulated disability, or had an active MRI scan) or a negative composite endpoint based on all 3 outcomes. A subgroup of patients ($n = 91$), scanned after treatment, were classified as MRI active or nonactive.

To assess differential lymphocyte reconstitution between groups, a linear mixed-effects regression method was undertaken with CD4/CD8/CD19/CD56/monocytes or total lymphocyte count as the outcome variable and relapse/disability/active MRI/composite score and time point as explanatory variables. A quadratic term (time point squared) was also included due to the observed relationship between time point and outcome. A separate linear mixed-effects model was fitted within each cycle. A continuous autoregressive (order 1) correlation structure was assumed for all models. Model coefficients are presented with 95% confidence intervals and p values. A Fisher exact test was used to assess whether a CD4 count of 388.5×10^6 /mL or greater at 12 months predicts disease activity, either clinically or radiologically. The standard 5% significance level was used throughout, and no adjustment made for multiple testing in order to avoid inflating the type II error rate. The linear mixed-effects regression method was implemented in *R* software⁸ using the nlme package.^{9,10} *R* software was also used to compute Fisher exact tests. All other analyses were performed in GraphPad PRISM (version 5.00 for Windows; www.graphpad.com).

RESULTS Study population characteristics. Data were derived from 108 patients, of whom 73 (67.6%) were female. The median follow-up from first treatment was 99 months (interquartile range [IQR] 74.75–117.25). The mean age of patients at first treatment with alemtuzumab was 32.8 years (SD 7.99). The median EDSS at baseline was 3.0 (IQR 1.5–4.75). Mean relapse frequency prior to treatment was 1.7 relapses per annum (SD 0.81).

Lymphocyte reconstitution. As previously reported,^{5,8,11} treatment with alemtuzumab led to profound pan-lymphocyte depletion, followed by differential recovery. CD19 lymphocytes reached the LLN most rapidly, with a median recovery time of 3 months (IQR 3–6). The intervals for CD8 and CD4 lymphocytes were median times of 19.5 (IQR 10–34.5) and 32 (IQR 21.75–41) months, respectively.

Clinical outcomes. The total number of patients who experienced at least 1 relapse during the follow-up period was 56 (51.85%). The mean relapse frequency posttreatment was 0.17 relapses per annum, equating to an 89.8% reduction in the annualized relapse rate

compared to pretreatment. Twenty-eight patients (25.9%) met the definition for sustained accumulation of disability. Ninety-one patients had an MRI scan: 16 individuals (17.6%) had an active scan (new T2/enhancing lesions) at some point during the follow-up period (see tables e-1 and e-2 on the *Neurology*[®] Web site at Neurology.org for a detailed breakdown of each alemtuzumab cycle).

Association of peripheral mononuclear cell subsets with disease activity. Relapse. Within each treatment cycle, there was no difference in the number of CD4 T cells, CD8 T cells, CD19 B cells, CD56 NK cells, or monocytes between those with and without clinically defined relapses (figure 1 for cycles 1-3, figure e-1 for cycle 4, and table 1; data not shown for NK cells and monocytes). Using the Fisher exact test, we found no association between a CD4 count of $>388.5 \text{ cells} \times 10^6/\text{mL}$ at 12 months and risk of relapse ($p = 0.28$). Given the possibility that relapses within the first few months of treatment may be due to lymphocytes that have already entered the CNS,¹² we looked at timing of relapses following cycle 2 (chosen as it is the most informative cycle in terms of patient numbers, number of relapses, and length of follow-up). Only 3 out of 106 patients relapsed within 2 months of treatment,

and of these, 2 went on to have additional relapses within cycle 2, leaving only one patient who was potentially misclassified using our method. Given this, we are confident in our conclusions.

MRI activity. Within each treatment cycle, there was no difference in the number of CD19 B cells, CD56 NK cells, or monocytes between those with and without active MRI scans (figure 2 for cycles 1-3, figure e-1 for cycle 4, and table 1; data not shown for NK cells and monocytes). CD4 cells ($p = 0.016$) and CD8 cells ($p = 0.008$) were found to be higher (on average by 0.146 and $0.125 \times 10^9/\text{mL}$ cells, respectively) in the active MRI group ($n = 5$) vs the inactive group ($n = 28$) within treatment cycle 3. No difference was found in any other treatment cycle; indeed, in cycles 1 and 2 (the most informative periods numerically), the trend was in the opposite direction (figure 2, table 1). Using the Fisher exact test, we found an association between a CD4 cell count of $>388.5 \times 10^6/\text{mL}$ at 12 months and the risk of having an active MRI scan (overall $p = 0.02$). However, further analysis of this result demonstrated that the difference was driven by patients within cycle 3 ($p < 0.0001$), with no difference observed within cycles 1 ($p = 1.0$), 2 ($p = 0.91$), or 4 ($p = 0.05$).

Disability accumulation. Within each treatment cycle, there was no difference in the number of

Figure 1 Comparison of CD4+, CD8+, and CD19+ cell counts after each cycle of alemtuzumab in patients with and without on-study relapses

Patients were defined as having relapsed (shown in red) if they developed neurologic symptoms attributable to multiple sclerosis lasting >48 hours with an objective change in neurologic examination in the absence of infection. Cell units are $\times 10^9/\text{L}$. Error bars indicate SD.

Table 1 Comparison of CD4+, CD8+, and CD19+ counts after each cycle of alemtuzumab in those with and without active disease

	Cycle	CD4			CD8			CD19		
		Coefficient	95% CI	p Value	Coefficient	95% CI	p Value	Coefficient	95% CI	p Value
Relapse	1	0.003	0.028 to 0.034	0.859	−0.020	−0.069 to 0.030	0.438	0.025	−0.026 to 0.077	0.330
	2	−0.029	−0.075 to 0.017	0.209	−0.011	−0.051 to 0.028	0.577	0.040	−0.007 to 0.087	0.095
	3	−0.009	−0.083 to 0.065	0.806	0.037	−0.017 to 0.090	0.173	0.005	−0.069 to 0.079	0.901
	4	−0.042	−0.333 to 0.248	0.741	−0.046	−0.255 to 0.163	0.620	−0.031	−0.376 to 0.314	0.839
MRI	1	−0.053	−0.117 to 0.012	0.104	−0.071	−0.168 to 0.027	0.144	0.011	−0.124 to 0.146	0.865
	2	−0.007	−0.094 to 0.080	0.873	−0.026	−0.116 to 0.063	0.558	0.010	−0.086 to 0.106	0.831
	3	0.146	0.029 to 0.264	0.016 ^a	0.125	0.035 to 0.214	0.008 ^a	0.029	−0.101 to 0.159	0.653
	4	0.068	−0.239 to 0.375	0.606	0.107	−0.134 to 0.348	0.319	−0.228	−0.588 to 0.131	0.171
Disability	1	−0.063	−0.103 to −0.024	0.002 ^a	−0.008	−0.076 to 0.060	0.813	0.042	−0.027 to 0.111	0.226
	2	−0.041	−0.099 to 0.016	0.154	−0.009	−0.057 to 0.039	0.709	0.005	−0.055 to 0.065	0.861
	3	−0.028	−0.114 to 0.058	0.522	−0.022	−0.084 to 0.040	0.473	−0.001	−0.087 to 0.084	0.977
	4	−0.204	−0.546 to 0.139	0.203	−0.104	−0.374 to 0.166	0.392	−0.054	−0.508 to 0.399	0.784
Composite	1	−0.019	−0.047 to 0.009	0.179	−0.004	−0.050 to 0.041	0.860	0.013	−0.033 to 0.060	0.571
	2	−0.028	−0.074 to 0.018	0.233	0.002	−0.035 to 0.039	0.923	0.021	−0.025 to 0.068	0.367
	3	−0.022	−0.095 to 0.051	0.550	0.021	−0.032 to 0.074	0.432	0.004	−0.069 to 0.077	0.915
	4	−0.285	−0.548 to −0.023	0.037 ^a	−0.184	−0.390 to 0.022	0.073	−0.107	−0.548 to 0.335	0.587

Abbreviation: CI = confidence interval.

For each cycle, patients were defined as active or not based on clinical relapse, MRI activity, disability acquisition, and the composite endpoint. A linear mixed-effects regression method was used with CD4+, CD8+, CD19+, CD56+ NK cells, or monocytes as the outcome variable, and with relapse, disability, MRI activity, or composite score and time point as explanatory variables. A quadratic term (time point squared) was also included due to the observed relationship between time point and outcome. A separate linear mixed-effects model was fitted within each cycle. A continuous autoregressive (order 1) correlation structure was assumed for all models. Model coefficients are presented with 95% CIs and p values are shown for CD4+, CD8+, and CD19+ cells (other subpopulations are reported in the text).

^a5% significance level reached.

CD8 T cells, CD19 B cells, CD56 NK cells, or monocytes between those with and without accumulation of disability (figure 3 for cycles 1–3, figure e-1 for cycle 4, and table 1). CD4 T cells were found to be lower in patients who accumulated disability in cycle 1 (adjusted mean difference across the cycle 0.063×10^9 ; $p = 0.002$). No difference was found in any other treatment cycle, although the trend was in the same direction (figure 3, table 1).

Composite. Within each treatment cycle, there was no difference in the number of CD8 T cells, CD19 B cells, CD56 NK cells, or monocytes between those who did and did not reach the composite end point (table 1; data not shown for nonlymphocyte cell populations). Within cycle 4, CD4 T cells were found to be lower in patients who met the composite end point compared to those who did not. No difference was found in any other treatment cycle (table 1).

DISCUSSION Using a much larger cohort and more prolonged follow-up, we fail to confirm the claim that accelerated CD4 T cell recovery after treatment is a biomarker for recurrent MS disease activity following lymphocyte depletion with alemtuzumab. We also find no evidence that a CD4 T-cell count

of greater than 388.5×10^6 cells/mL at 12 months has utility in selecting a group of patients who may benefit from more intensive monitoring or perhaps even prophylactic repeat dosing.

There are a number of differences between our work and the previous report.⁸ First, our cohort is larger (108 vs 56 patients) with a longer duration of follow-up (median follow up of 99 months [IQR 74.75–117.25] vs 55 months [IQR 24–115]). Although both studies selected patients with active RRMS, baseline MS disease activity was somewhat higher in the previous study (annualized relapse rate of 2.6 SD 0.9 vs 1.7 SD 0.8); however, few of their patients experienced disease activity post alemtuzumab (probably reflecting their shorter follow-up): only 8/56 experienced a clinical relapse, with a further 4 patients showing MRI disease activity alone; this small number of data points makes the study susceptible to extreme outliers. Unlike the previous study, we did not perform routine MRI brain scans at month 24. As a consequence, analysis of MRI outcome is based on data from fewer patients (19 for cycle 1, 59 for cycle 2, 33 for cycle 3, and 10 for cycle 4); this is a limitation of our study.

However, these differences do not explain why our 2 studies have reached opposite conclusions; this is best

Figure 2 Comparison of CD4+, CD8+, and CD19+ cell counts after each cycle of alemtuzumab in patients with and without on-study active MRI scans

Patients were defined as having an active MRI scan (shown in red) if they had acquired new T2 lesions or enhancing lesions. Cell units are $\times 10^9/L$. Error bars indicate SD.

explained by weaknesses in their statistical methods. First, they did not account for repeated treatments; only cell counts from the most recent alemtuzumab dose were analyzed: post cycle 2 CD4 counts for those who remain in remission were compared to post cycle 3 counts for those with active disease prompting redosing and CD4 counts post cycle 3 were then correlated with disease activity prior to cycle 3 and used to predict an event that had already occurred. This method assumes that reconstitution is identical after each round of treatment, representing a major limitation of their study. We controlled for this bias by looking at reconstitution and disease activity after and within each treatment cycle. Due to complexity of the analysis, the timing of the event within each cycle is still not accounted for. Secondly, the previous report compared mean cell counts at multiple time points using Student *t* tests, or Mann-Whitney *U* when non-normally distributed, without taking into account multiple nonindependent observations per patient (an individual's CD4 count at month 12 is not independent of the month 9 count, and so on). Furthermore, *p* values were not corrected for multiple comparisons, of which there were many, so it is likely that some of the statistically significant results occurred by chance; when we repeated the analysis using our data, no *p* value survived correction (data not shown).

The wish to identify a biomarker for recurrent disease activity after alemtuzumab is to be welcomed. This would reduce the need to monitor patients at low risk of relapse and allow the preemptive treatment of high-risk patients. Although CD4 counts may be an attractive candidate—they are readily measurable and T cells are undoubtedly involved in disease pathogenesis—given the complex nature of the immune system, it is not surprising that peripheral CD4 counts alone do not predict CNS inflammation (indeed, it is known that selective anti-CD4-depleting therapies do not suppress disease activity in MS¹³). Also, after alemtuzumab treatment, composition of the circulating immune repertoire is radically altered. For example, for at least 6 months following each cycle, the CD4 T-cell pool is dominated by memory cells, particularly those with a regulatory phenotype ($CD4^+CD45RA-CD35hiFoxP3+IL-7Rlo$).¹⁴ Self evidently, investing confidence in a single measure of a major cellular constituent of peripheral blood disregards the complexity of the immunopathogenesis of MS and is misplaced.

Arguably, our data do not prove or disprove whether long-term disease stability is associated with lower CD4 counts, as patients with clinical or radiologic evidence of disease activity are automatically retreated. However, it is our position that peripheral

Figure 3 Comparison of CD4+, CD8+, and CD19+ cell counts after each cycle of alemtuzumab in patients with and without acquisition of disability

Patients were deemed to have met the definition of sustained accumulation of disability if their Expanded Disability Status Scale increased by ≥ 1.5 points from a baseline of 0, or by ≥ 1.0 points from a baseline of ≥ 1.0 . Patients meeting this definition are shown in red. Cell units are $\times 10^9/L$. Error bars indicate SD.

CD4 counts have no utility in predicting MS disease activity after alemtuzumab, and we strongly advise neurologists against using them to personalize treatment protocols. In particular, CD4 counts should not be used as a marker of the need for preemptive retreatment, thereby exposing patients to potential risk.^{1–3} Our cautionary message, refuting the claims of the previous report,⁸ is timely since alemtuzumab will soon be entering the clinic as a treatment for active RRMS.

AUTHOR CONTRIBUTIONS

Dr. Onajite Kousin-Ezewu designed and conducted the study, analyzed data in the study, interpreted data in the study, and drafted and revised the manuscript. Dr. Laura Azzopardi conducted the study and interpreted data in the study. Mr. Richard Parker analyzed data in the study. Dr. Orla Tuohy conducted the study. Prof Alastair Compston revised the manuscript. Dr. Alasdair J. Coles designed the study and revised the manuscript. Dr. Joanne L. Jones designed the study, analyzed data in the study, interpreted data in the study, and revised the manuscript.

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