

ORIGINAL ARTICLE

Alemtuzumab vs. Interferon Beta-1a in Early Multiple Sclerosis

The CAMMS223 Trial Investigators*

ABSTRACT

BACKGROUND

Alemtuzumab, a humanized monoclonal antibody that targets CD52 on lymphocytes and monocytes, may be an effective treatment for early multiple sclerosis.

METHODS

In this phase 2, randomized, blinded trial involving previously untreated, early, relapsing–remitting multiple sclerosis, we assigned 334 patients with scores of 3.0 or less on the Expanded Disability Status Scale and a disease duration of 3 years or less to receive either subcutaneous interferon beta-1a (at a dose of 44 μ g) three times per week or annual intravenous cycles of alemtuzumab (at a dose of either 12 mg or 24 mg per day) for 36 months. In September 2005, alemtuzumab therapy was suspended after immune thrombocytopenic purpura developed in three patients, one of whom died. Treatment with interferon beta-1a continued throughout the study.

RESULTS

Alemtuzumab significantly reduced the rate of sustained accumulation of disability, as compared with interferon beta-1a (9.0% vs. 26.2%; hazard ratio, 0.29; 95% confidence interval [CI], 0.16 to 0.54; $P < 0.001$) and the annualized rate of relapse (0.10 vs. 0.36; hazard ratio, 0.26; 95% CI, 0.16 to 0.41; $P < 0.001$). The mean disability score on a 10-point scale improved by 0.39 point in the alemtuzumab group and worsened by 0.38 point in the interferon beta-1a group ($P < 0.001$). In the alemtuzumab group, the lesion burden (as seen on T_2 -weighted magnetic resonance imaging) was reduced, as compared with that in the interferon beta-1a group ($P = 0.005$). From month 12 to month 36, brain volume (as seen on T_1 -weighted magnetic resonance imaging) increased in the alemtuzumab group but decreased in the interferon beta-1a group ($P = 0.02$). Adverse events in the alemtuzumab group, as compared with the interferon beta-1a group, included autoimmunity (thyroid disorders [23% vs. 3%] and immune thrombocytopenic purpura [3% vs. 1%]) and infections (66% vs. 47%). There were no significant differences in outcomes between the 12-mg dose and the 24-mg dose of alemtuzumab.

CONCLUSIONS

In patients with early, relapsing–remitting multiple sclerosis, alemtuzumab was more effective than interferon beta-1a but was associated with autoimmunity, most seriously manifesting as immune thrombocytopenic purpura. The study was not powered to identify uncommon adverse events. (ClinicalTrials.gov number, NCT00050778.)

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MULTIPLE SCLEROSIS TYPICALLY FOLLOWS a relapsing–remitting course, but most patients eventually convert to a secondary progressive phase characterized by deficits that increase in the absence of further relapses. This clinical evolution reflects the complex interplay of focal inflammation, demyelination, and axonal degeneration in the central nervous system. Current disease-modifying treatments decrease the frequency of relapse and modestly reduce the accumulation of disability but have not been shown to prevent secondary progression.¹ New agents that combine improved efficacy with acceptable safety need to be identified. The humanized monoclonal antibody alemtuzumab (Campath-1H; Campath, or MabCampath; Genzyme) targets CD52 on lymphocytes and monocytes. Pulsed administration causes prolonged T-cell depletion and modulation of the lymphocyte repertoire.²

Since 1991, studies of alemtuzumab in the treatment of patients with secondary progressive multiple sclerosis have suggested efficacy in the suppression of relapse but not in preventing the continued progression of disability.³ Although few infections occurred, autoimmunity developed in some patients several months after administration of the drug.⁴ Subsequent open-label studies in relapsing–remitting disease showed that alemtuzumab stabilized and even improved existing deficits.² On the basis of these observations emerged hypotheses that the secondary progressive phase of the disease might be attributable to postinflammatory neurodegeneration and that immunotherapy would influence long-term disability only if administered early in the disease course. These concepts informed the design of our blinded, phase 2, randomized trial comparing two doses of alemtuzumab with subcutaneous interferon beta-1a (Rebif, EMD Serono and Pfizer) in previously untreated patients with early, relapsing–remitting multiple sclerosis.

METHODS

PATIENTS

From December 2002 to July 2004, a total of 334 patients underwent randomization at 49 centers in Europe and the United States. The last patient started treatment in September 2004. Each patient provided written informed consent.

Eligibility criteria were a diagnosis of relapsing–remitting multiple sclerosis (on the basis of

the McDonald criteria⁵) with an onset of symptoms no more than 36 months before the time of screening; at least two clinical episodes during the previous 2 years; a score of 3 or less on the Expanded Disability Status Scale (EDSS),⁶ which ranges from 0 to 10, with higher scores indicating greater disability; and one or more enhancing lesions, as seen on at least one of up to four monthly cranial magnetic resonance imaging (MRI) scans. Key exclusion criteria were previous disease-modifying treatments, a history of clinically significant autoimmunity, or the presence of serum antithyrotropin-receptor antibodies.

STUDY DESIGN AND RANDOMIZATION

Eligible patients were randomly assigned in a 1:1:1 ratio to receive alemtuzumab (at a dose of either 12 mg per day or 24 mg per day) or interferon beta-1a with the use of the Pocock and Simon minimization algorithm⁷ to balance the study groups with regard to age (<30 years or ≥30 years), sex, and baseline EDSS score (<2.0 or ≥2.0). Alemtuzumab was given by intravenous infusion on 5 consecutive days during the first month and on 3 consecutive days at months 12 and 24 (the latter at the treating physicians' discretion if the CD4+ T-cell count was ≥100×10⁶ cells per liter). Interferon beta-1a (at a dose of 44 μg) was administered subcutaneously three times weekly after dose escalation. All patients received 1 g of intravenous methylprednisolone for 3 days at baseline and at months 12 and 24, coinciding with infusion cycles as premedication for those receiving alemtuzumab. Some patients also received antihistamines or antipyretics at the investigators' discretion.

STUDY OUTCOMES AND PROCEDURES

EDSS scores were determined quarterly in a blinded fashion by a neurologist who also adjudicated possible relapses. Patients wore clothing that covered injection sites. The effectiveness of blinding was assessed at the end-of-study visit. Safety was assessed quarterly by the treating neurologist, who was aware of study-group assignment.

The coprimary measures of efficacy were the time to sustained accumulation of disability and the rate of relapse. Disability was assessed according to the ordinal EDSS score. A sustained accumulation of disability was defined as an increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more; all scores

were confirmed twice during a 6-month period. The onset of a sustained level of disability was timed to the first recorded increase in the EDSS score aside from relapse. Patients with an increased level of disability could be discontinued from the study. A relapse was defined as new or worsening symptoms with an objective change in neurologic examination attributable to multiple sclerosis that lasted for at least 48 hours, that were present at normal body temperature, and that were preceded by at least 30 days of clinical stability.

Secondary outcomes were the proportion of patients who did not have a relapse, changes in lesion burden (as seen on T₂-weighted MRI), and brain volume (as measured by the Losseff method on T₁-weighted MRI⁸). MRI scans were performed annually and interpreted by a neuroradiologist at Perceptive Informatics who was unaware of assignments to study groups.

Thyroid function and levels of antithyrotropin-receptor antibodies and lymphocyte subpopulations were measured quarterly at a central laboratory (Cirion Clinical Trial Services and Charles River Laboratories). Serum-binding antibodies against alemtuzumab were measured with the use of a validated enzyme-linked immunosorbent assay (ELISA)⁹ at BioAnaLab. There was no active monitoring for progressive multifocal leukoencephalopathy. Criteria for the diagnosis of immune thrombocytopenia were a single confirmed platelet count of fewer than 50,000 per microliter without clumping or a platelet count of more than 50,000 but fewer than 100,000 per microliter on at least two consecutive occasions during a period of at least 1 month, with normal hemoglobin, neutrophil, and eosinophil counts; an absence of splenomegaly; and a normal peripheral-blood smear (apart from thrombocytopenia). All adverse events with an onset up to 36 months are reported. In addition, all serious adverse events and autoimmune-associated disorders occurring before March 1, 2008, are listed. A subsequent adverse event of Burkitt's lymphoma not associated with Epstein-Barr virus (EBV) is also included in this report.

STATISTICAL ANALYSIS

On the basis of the literature,²⁻¹⁶ we determined that 285 patients would be needed to provide a power of 75% to detect a treatment effect at 36 months, assuming a rate of sustained disability of 12% in the alemtuzumab group and of 30% in

the group receiving interferon beta-1a with a two-sided test and a significance level of 2% (with a Bonferroni adjustment for two alemtuzumab groups and a significance level of 1% for the comparison of relapse rates). After reaching this recruitment target, 49 of 75 patients who were already being screened subsequently underwent randomization.

Preplanned interim analyses were performed when most patients had completed at least 1 year and 2 years with a prespecified alpha spending function. Disclosure of these results formed part of safety announcements by the sponsor in September 2005 and 2006. After the interim analyses, P values of less than 0.016 and 0.004 were considered to have statistical significance for the rates of sustained disability and relapse, respectively (for details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

Treatment effects were compared with respect to the time to sustained accumulation of disability with the use of a proportional-hazards model and to the rate of relapse with the use of the Andersen-Gill model with robust variance estimation.¹⁰ Covariates for these models included study-group indicators, country, and baseline EDSS score. The proportion of patients with relapse-free survival was assessed with the use of logistic regression. The estimated percentage of patients with sustained disability or relapse was generated by the Kaplan-Meier method. The annualized rate of relapse was estimated with the use of Poisson regression. The number of patients who would need to be treated with alemtuzumab instead of interferon beta-1a to prevent one patient from having a relapse or sustained disability was calculated according to the proportion of patients who did not have these outcomes at month 36.¹¹ Comparisons of EDSS scores were based on a repeated-measures analysis of covariance. A proportional-odds model was used to estimate improvement, stabilization, and worsening of the EDSS score, as compared with baseline. The percent change from baseline on MRI was analyzed with the use of the Wilcoxon-Mann-Whitney test and the multivariate Wei-Lachin test^{12,13} during the entire 36-month period. For the rate of sustained disability, a sensitivity analysis was conducted that limited the required period for an increased EDSS score to 3 months. Fisher's exact test and Poisson regression were

used for the analysis of adverse events and event rates, respectively. The reported P values are two-sided and were not adjusted for multiple testing. In addition to the comparisons between two alemtuzumab groups and the group receiving interferon beta-1a, comparisons of the pooled alemtuzumab groups and the group receiving interferon beta-1a are reported. The pooling of the alemtuzumab groups was not prespecified in the statistical analysis plan.

The protocol was designed by the lead academic authors and was approved by local review boards or the ethics committee at each center. Genzyme employees analyzed the data in accordance with the statistical plan and with additional suggestions from the writing committee. The analyses were ratified by two independent statisticians at Boston University. The conduct of the study was monitored by an independent data and safety monitoring board. The lead academic authors vouch for the completeness and veracity of the data and analyses.

RESULTS

STUDY POPULATION

Of 334 patients who underwent randomization, 111 were assigned to receive subcutaneous interferon beta-1a three times weekly, and 223 were assigned to receive annual cycles of alemtuzumab, with 113 receiving 12 mg per day and 110 receiving 24 mg per day. One patient who received alemtuzumab was included in the safety analysis but was excluded from the efficacy analyses because the initial diagnosis of multiple sclerosis was incorrect, and the patient received the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) during the study. Baseline demographic and clinical characteristics were similar in the three treatment groups (Table 1). The enrollment and outcomes of patients are shown in Figure 1. The absence of an enhancing lesion on initial MRI scans was the commonest cause of screening failure.

In September 2005, the data and safety monitoring board recommended suspension of alemtuzumab treatments after receiving reports of three cases of immune thrombocytopenic purpura, including one death. All safety and efficacy assessments proceeded as planned, and patients who were receiving interferon beta-1a continued to

receive the drug. At the time of dose suspension, only 2 eligible patients (1%) had not received the second cycle of alemtuzumab at month 12, whereas 155 patients (75%) were precluded from receiving the third cycle of alemtuzumab at month 24. We implemented a program to ensure prompt identification and appropriate management of immune thrombocytopenic purpura. This program included education for patients and physicians, monthly blood counts, and regular contact with patients, which included discussion about symptoms and signs of immune thrombocytopenic purpura. Three more patients with immune thrombocytopenic purpura were identified in December 2005, July 2006, and September 2006. Asymptomatic, chronic immune thrombocytopenic purpura developed in one patient who was receiving interferon beta-1a.

More patients discontinued interferon beta-1a than alemtuzumab, principally because of a lack of efficacy and adverse events, so that only 59% of the original group of patients receiving interferon beta-1a completed the 36-month study, as compared with 83% of patients receiving alemtuzumab. At the end of the study review, 90% and 91% of raters remained unaware of assignments to the group receiving interferon beta-1a and the group receiving alemtuzumab, respectively.

CLINICAL EFFICACY

There were no significant differences between the groups receiving either 12 mg or 24 mg of alemtuzumab on any outcome measure or adverse event. Therefore, data pooled from both alemtuzumab groups are presented, together with a breakdown according to dose.

Disability

As compared with interferon beta-1a, alemtuzumab reduced the risk of sustained disability by 71% (hazard ratio, 0.29; 95% confidence interval [CI], 0.16 to 0.54; $P < 0.001$) (Table 2 and Fig. 2A). For the 12-mg dose, the risk of sustained disability was reduced by 75% (hazard ratio, 0.25; 95% CI, 0.11 to 0.57; $P < 0.001$); for the 24-mg dose, the risk reduction was 67% (hazard ratio, 0.33; 95% CI, 0.16 to 0.69; $P = 0.003$). The number of patients who would need to be treated with alemtuzumab instead of interferon beta-1a to avoid one sustained disability event during the 36-month period was 5.8 (5.6 for the 12-mg dose and 6.0 for the 24-mg dose). In sensitivity analysis of the risk of sustained

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Interferon Beta-1a (N=111)	Alemtuzumab†		All Patients (N=222)
		12-mg Dose (N=112)	24-mg Dose (N=110)	
Demographic				
Age — yr	32.8±8.8	31.9±8.0	32.2±8.8	32.1±8.4
Median	31	31	31	31
Range	18–60	18–49	18–54	18–54
Female sex — %	64.0	64.3	64.5	64.4
White race — %‡	90.1	91.1	89.1	90.1
Level of disability				
EDSS score at baseline§				
Mean	1.9±0.83	1.9±0.74	2.0±0.73	2.0±0.74
Median	2.0	2.0	2.0	2.0
Range	0–3.5	0–3.0	0–3.5	0–3.5
Subgroup of scores — no. (%)				
0	8 (7.2)	4 (3.6)	5 (4.5)	9 (4.1)
>0–1.5	37 (33.3)	40 (35.7)	36 (32.7)	76 (34.2)
>1.5–2.0	28 (25.2)	30 (26.8)	30 (27.3)	60 (27.0)
>2.0–3.5	38 (34.2)	38 (33.9)	39 (35.5)	77 (34.7)
History of relapse				
Time since first relapse — yr				
Median	1.4	1.3	1.2	1.3
Range	0.2–6.3	0.1–3.5	0.3–3.2	0.1–3.5
Total no. of relapses	293	301	290	591
Relapse in previous 2 yr — no. (%)				
0	0	2 (1.8)	1 (0.9)	3 (1.4)
1	8 (7.2)	6 (5.4)	13 (11.8)	19 (8.6)
2	73 (65.8)	58 (51.8)	56 (50.9)	114 (51.4)
≥3	30 (27.0)	46 (41.1)	40 (36.4)	86 (38.7)

* Plus–minus values are means ±SD. EDSS denotes Expanded Disability Status Scale.

† One patient who received alemtuzumab was excluded from the efficacy analyses (but was included in the safety analysis) because the initial diagnosis of multiple sclerosis was incorrect.

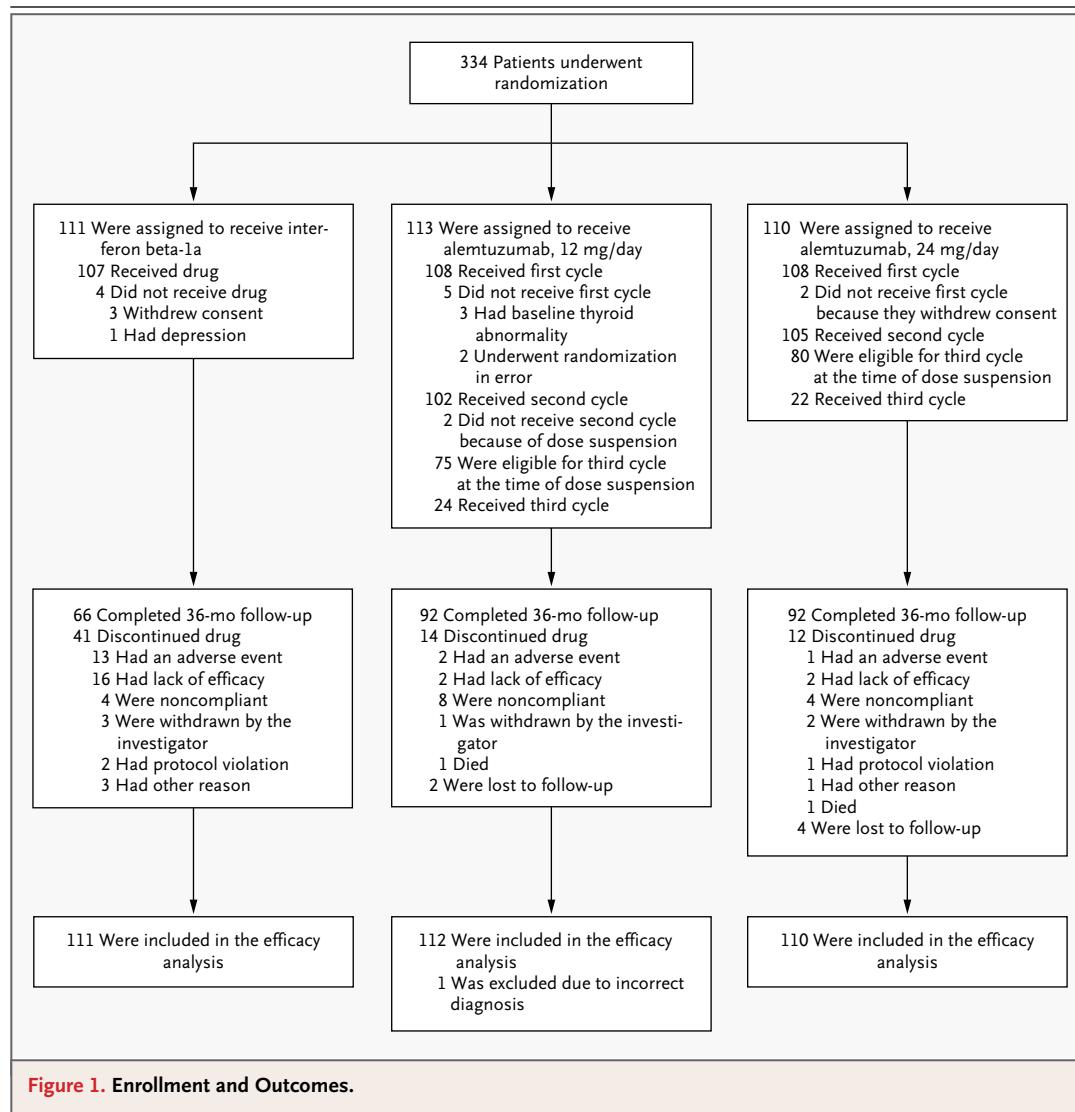
‡ Race was self-reported.

§ EDSS scores range from 0 to 10, with higher scores indicating greater disability. The minimum EDSS interval is 0.5 for detecting a clinical difference.

disability at 3 months, the risk reduction was 64% (hazard ratio, 0.36; 95% CI, 0.21 to 0.60; $P<0.001$).

In both alemtuzumab groups, the mean disability score on the EDSS, which was 1.9 points at baseline, improved by 0.39 point (95% CI, 0.23 to 0.55) at 36 months: 0.32 point for the 12-mg dose ($P=0.006$) and 0.45 point for the 24-mg dose ($P=0.001$). During the same time, the mean dis-

ability score worsened by 0.38 point (95% CI, 0.13 to 0.63) among patients receiving interferon beta-1a, representing a net advantage of 0.77 point (95% CI, 0.48 to 1.06; $P<0.001$) among patients receiving alemtuzumab (Table 2 and Fig. 2C). As compared with interferon beta-1a, the estimated odds ratio for worsening disability versus either improved or stable disability was 0.41 (95% CI,



0.24 to 0.69) for the 12-mg dose of alemtuzumab and 0.33 (95% CI, 0.19 to 0.56) for the 24-mg dose ($P < 0.001$ for both comparisons).

Relapse

As compared with interferon beta-1a, alemtuzumab reduced the rate of relapse by 74% (hazard ratio, 0.26; 95% CI, 0.16 to 0.41; $P < 0.001$) (Table 2 and Fig. 2B); both alemtuzumab doses were effective, with a reduction of 69% (95% CI, 48 to 82) for the 12-mg dose and 79% (95% CI, 60 to 89) for the 24-mg dose ($P < 0.001$ for both comparisons). The annualized relapse rate at 36 months was 0.36 for interferon beta-1a and 0.10 for alemtuzumab (0.11 for the 12-mg dose and 0.08 for the 24-mg

dose). The proportion of patients who remained relapse-free at 36 months was 52% for interferon beta-1a and 80% for alemtuzumab (77% for the 12-mg dose and 84% for the 24-mg dose; $P < 0.001$ for both comparisons) (Table 2). The number of patients who would need to be treated with alemtuzumab instead of interferon beta-1a to prevent 1 patient from having a relapse at 36 months was 3.5 (3.9 and 3.1 for the 12-mg dose and 24-mg dose, respectively).

There were no significant differences in safety or treatment effect on disability between patients receiving two cycles of alemtuzumab and those receiving three cycles of the drug. However, there was evidence of the waning of treatment efficacy

on the rate of relapse. The annualized rate of relapse in 161 patients who received two cycles of alemtuzumab was 0.16 in months 24 to 36, an increase from 0.07 for months 0 to 12 and 0.06 for months 12 to 24. This rate was significantly reduced, as compared with the rate of 0.34 in patients receiving interferon beta-1a between months 24 and 36 ($P=0.01$). Among 45 patients who received three cycles of alemtuzumab, there was only one relapse between months 24 and 36 (Fig. 2D).

EFFICACY ON MRI

From baseline to 36 months, there was a reduction in the volume of lesions, as seen on T₂-weighted MRI, in all three study groups (Table 2). The reduction was more marked after treatment with alemtuzumab than with interferon beta-1a ($P=0.005$), with significant reductions from baseline at months 12 ($P=0.01$) and 24 ($P=0.005$). The differences in median change at month 36 were not significant. Of note, the sample size for the

Table 2. Measures of Disability, Relapse, and Radiologic Outcomes.*

Outcome	Interferon Beta-1a (N=111)		Alemtuzumab†	
		12-mg Dose (N=112)	24-mg Dose (N=110)	All Patients (N=222)
Disability				
Sustained accumulation for 6 mo				
Patients with outcome — no. (%)‡	24 (26.2)	8 (8.5)	10 (9.5)	18 (9.0)
Hazard ratio (95% CI)		0.25 (0.11 to 0.57)	0.33 (0.16 to 0.69)	0.29 (0.16 to 0.54)
Treatment effect (95% CI) — %		75 (43 to 89)	67 (31 to 84)	71 (46 to 84)
P value		<0.001	0.003	<0.001
Sustained accumulation for 3 mo				
Patients with outcome — no. (%)‡	30 (32.7)	16 (16.3)	12 (11.4)	28 (13.8)
Hazard ratio (95% CI)		0.42 (0.23 to 0.77)	0.30 (0.15 to 0.59)	0.36 (0.21 to 0.60)
Treatment effect (95% CI)		58 (23 to 77)	70 (41 to 85)	64 (40 to 79)
P value		0.005	<0.001	<0.001
Change in mean EDSS score from baseline§				
Mean (95% CI)	0.38 (0.13 to 0.63)	-0.32 (-0.55 to -0.10)	-0.45 (-0.68 to -0.22)	-0.39 (-0.55 to -0.23)
P value	0.003	0.006	<0.001	<0.001
Change in EDSS score from baseline				
Total no. of patients	104	107	108	215
Score improved — no. (%)	35 (33.7)	58 (54.2)	65 (60.2)	123 (57.2)
Score stayed the same — no. (%)	26 (25.0)	25 (23.4)	23 (21.3)	48 (22.3)
Score declined — no. (%)	43 (41.3)	24 (22.4)	20 (18.5)	44 (20.5)
Odds ratio for worsening disability (95% CI)¶		0.41 (0.24 to 0.69)	0.33 (0.19 to 0.56)	0.37 (0.23 to 0.58)
Treatment effect (95% CI)		59 (31 to 76)	67 (44 to 81)	63 (42 to 77)
P value		<0.001	<0.001	<0.001
Relapse				
Total no. of events	89	34	25	59
Patients with any event — no.	45	24	17	41
Hazard ratio (95% CI)		0.31 (0.18 to 0.52)	0.21 (0.11 to 0.40)	0.26 (0.16 to 0.41)
Treatment effect (95% CI) — %		69 (48 to 82)	79 (60 to 89)	74 (59 to 84)
P value		<0.001	<0.001	<0.001
Annualized rate (95% CI)	0.36 (0.29 to 0.44)	0.11 (0.08 to 0.16)	0.08 (0.05 to 0.12)	0.10 (0.07 to 0.12)
Patients with no relapse — %‡	51.6	77.0	83.5	80.2

Table 2. (Continued.)

Outcome	Interferon Beta-1a (N=111)		Alemtuzumab†	
		12-mg Dose (N=112)	24-mg Dose (N=110)	All Patients (N=222)
Lesion load on T₂-weighted MRI				
No. of patients at baseline	102	106	107	213
0–12 mo				
No. of patients	91	96	100	196
% Change from baseline				
Median	–12.1	–17.7	–19.2	–18.3
Interquartile range	–29.4 to 16.1	–44.7 to 1.9	–36.4 to 1.3	–38.1 to 1.8
P value		0.02	0.03	0.01
0–24 mo				
No. of patients	75	91	96	187
% Change from baseline				
Median	–9.8	–21.2	–20.3	–20.4
Interquartile range	–30.3 to 21.7	–36.0 to –3.2	–41.6 to 4.5	–39.6 to 0.5
P value		0.01	0.02	0.005
0–36 mo				
No. of patients	60	80	87	167
% Change from baseline				
Median	–13.3	–18.2	–13.5	–16.4
Interquartile range	–28.5 to 19.0	–35.7 to 5.3	–34.9 to 10.0	–35.4 to 7.2
P value		0.21	0.40	0.24
P value for overall comparison‖		0.01	0.03	0.005
Brain volume on T₁-weighted MRI				
No. of patients at baseline	103	107	107	214
0–36 mo				
% Change from baseline				
Median	–1.8	–0.9	0	–0.5
Interquartile range	–5.0 to 0.9	–2.9 to 1.4	–2.7 to 1.5	–2.8 to 1.5
P value		0.16	0.04	0.05
12–36 mo				
% Change from baseline				
Median	–0.2	1.2	0.7	0.9
Interquartile range	–4.1 to 2.1	–2.1 to 3.4	–1.9 to 3.9	–2.1 to 3.9
P value		0.03	0.04	0.02

* Hazard ratios, treatment effects, and P values are all for the comparison between alemtuzumab and interferon beta-1A. EDSS denotes Expanded Disability Status Scale.

† One patient who received alemtuzumab was excluded from the efficacy analyses (but was included in the safety analysis) because the initial diagnosis of multiple sclerosis was incorrect.

‡ Percentages were calculated with the use of the Kaplan–Meier method.

§ EDSS scores range from 0 to 10, with higher scores indicating worse function.

¶ The odds ratio is for worsening disability versus either improved or stable disability.

‖ The P value is for a multivariate comparison of all time points calculated with the Wei–Lachin test.

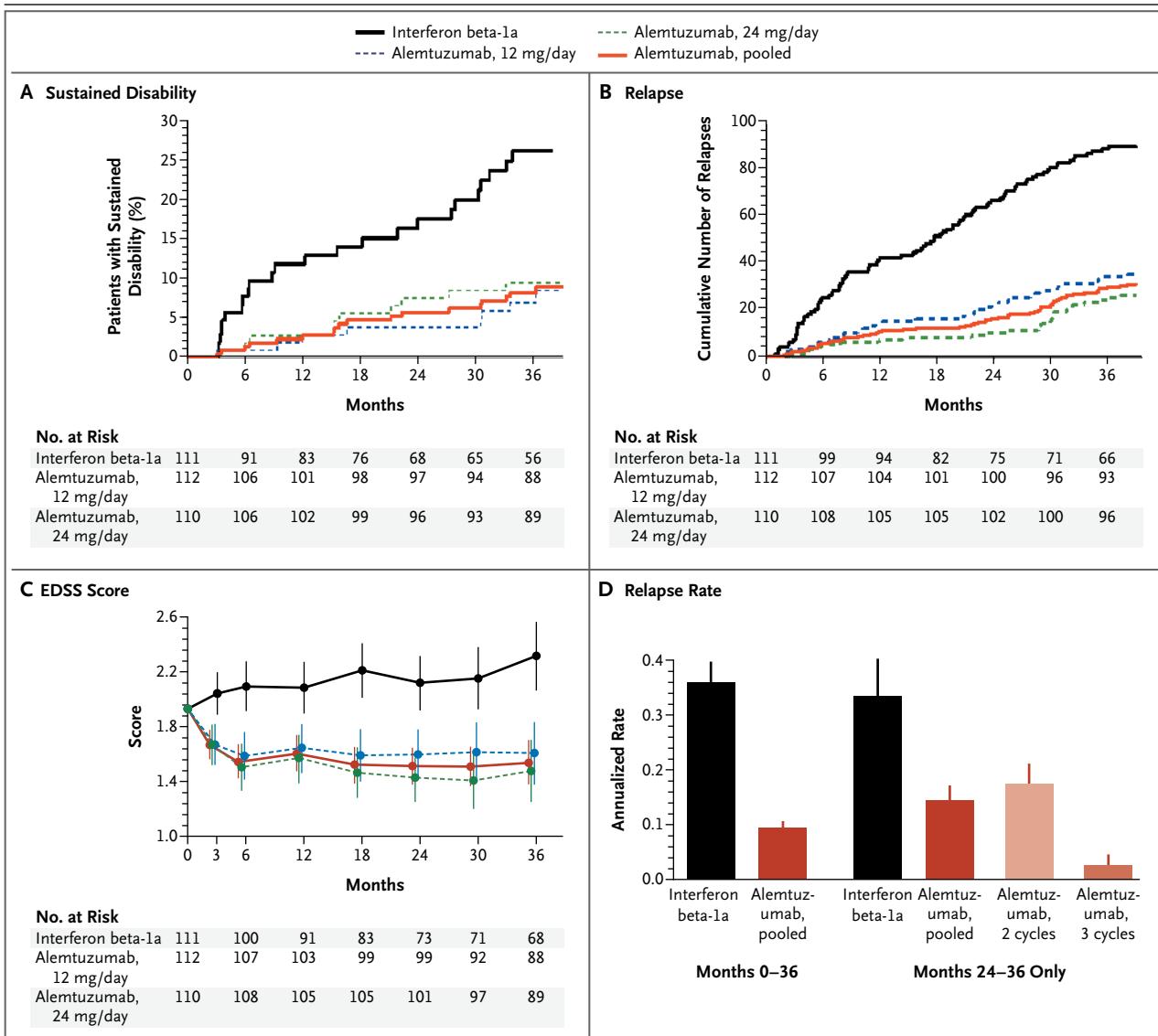


Figure 2. Efficacy Outcome Measures Regarding Disability and Relapse at 36 Months.

Panel A shows Kaplan–Meier curves for patients who reached the criteria for sustained accumulation of disability. Panel B shows the cumulative number of relapses. Panel C shows the estimated mean score on the Expanded Disability Status Scale (EDSS, which ranges from 0 to 10, with higher scores indicating greater disability) on the basis of repeated-measures analysis of covariance. The vertical lines represent 95% confidence intervals. Panel D shows the annualized relapse rate from baseline to 36 months for 222 patients who received aletuzumab and from month 24 to month 36 for 97 patients who received aletuzumab for two cycles and 45 patients who received aletuzumab for three cycles. Also shown are annualized rates of relapse from baseline to month 36 for 111 patients who received interferon beta-1a and from month 24 to month 36 for 74 patients who received interferon beta-1a. The annualized relapse rates were estimated with the use of Poisson regression analysis separately for patients who received a third cycle of therapy and for those who did not receive a third cycle. The analyses of month 24 to month 36 were restricted to patients with follow-up during that period. The vertical lines represent standard errors.

36-month analyses was reduced because of the number of patients who discontinued the study and the 26 patients who had missing or technically deficient MRI scans. The reduction in brain volume between baseline and month 36 was significantly less among patients receiving aletuzumab than among those receiving interferon beta-1a (–0.5% and –1.8%, respectively; $P=0.05$). Recognizing that atrophy measures may be confounded by early suppression of inflammatory

space-occupying lesions, we analyzed brain volume between months 12 and 36; this measure was reduced by 0.2% among patients receiving interferon beta-1a but was increased by 0.9% in those receiving alemtuzumab ($P=0.02$) (Table 2).

On clinical and MRI outcomes, alemtuzumab remained superior to interferon beta-1a after subgroup analyses according to study-site location, baseline EDSS score, lesion load on T₂-weighted MRI, cerebral volume on T₁-weighted MRI, sex, race, and age of patients (data not shown).

SAFETY AND SIDE EFFECTS

Almost all patients reported at least one adverse event, and the number who had serious adverse events was also similar among the three study groups (Table 3 and the Supplementary Appendix). There were two deaths, both in the alemtuzumab group. One patient who had several pre-existing cardiac risk factors died of cardiovascular disease. The other death was attributable to immune thrombocytopenic purpura. Three cancers (non-EBV-associated Burkitt's lymphoma, breast cancer, and cervical cancer in situ) were reported in patients in the alemtuzumab group, with onset ranging from 22 to 64 months after the first annual cycle; among patients receiving interferon beta-1a, one case of colon cancer was reported at 36 months (Table 3).

Serious infusion reactions occurred in three patients (1.4%) in the alemtuzumab group and led to discontinuation in one patient (0.5%). Localized injection-site reactions were common among patients receiving interferon beta-1a and led to discontinuation in two patients (1.9%). Abnormal liver-function tests were seen in 2.3% of patients in the alemtuzumab group and in 15.0% of those receiving interferon beta-1a, causing discontinuation of interferon beta-1a in three patients and grade 4 hepatic failure in one patient.

Mild-to-moderate infections, especially of the respiratory tract, were more common among patients in the alemtuzumab group than in those receiving interferon beta-1a. Recurrent oral herpes simplex virus type 1 was seen in three patients immediately after each cycle of alemtuzumab. Inactive tuberculosis was identified incidentally in one patient receiving the 24-mg dose of alemtuzumab. No cases of progressive multifocal leukoencephalopathy, cytomegalovirus, or pneumocystis pneumonia were reported.

Immune thrombocytopenic purpura developed

in six patients (2.8%) receiving alemtuzumab and one patient (0.9%) receiving interferon beta-1a ($P=0.43$). The index patient suffered a fatal brain hemorrhage before diagnosis. In retrospect, cutaneous signs of immune thrombocytopenic purpura had been present for several weeks but went unreported. Of the six patients receiving alemtuzumab in whom immune thrombocytopenic purpura developed, four were receiving the 24-mg dose (three patients after two cycles and one after three) and two were receiving the 12-mg dose (both after three cycles). Remission of immune thrombocytopenic purpura occurred without treatment in one patient, after corticosteroid therapy in two patients, and after rituximab therapy in two patients. Grade 2 thrombocytopenia developed in one patient after 3 months of receiving interferon beta-1a; the condition persisted despite the withdrawal of interferon beta-1a and remained at grade 1 at the end of the study after reintroduction of interferon beta-1a.

Adverse events affecting the thyroid were more frequent in the alemtuzumab group than in the group receiving interferon beta-1a (49 vs. 3) (Table 3); these events were associated with thyroid autoantibodies in 96% of affected patients and occurred up to 30 months after the last dose of a study drug. Three patients (1.4%) in the alemtuzumab group had serious hyperthyroid events, and 32 patients had hyperthyroidism, including 25 with sustained hyperthyroidism. Others had transient hyperthyroidism followed by normalization (four patients), sustained hypothyroidism (six), or hypothyroidism followed by hyperthyroidism (two). Four patients underwent thyroid ablation with radioactive iodine, and 24 were treated with antithyroid agents (3 only temporarily). Primary hypothyroidism developed in 10 patients. In total, 18 patients required long-term thyroid-replacement therapy. Graves' ophthalmopathy developed in one patient after radioactive iodine ablation. (Numbers of patients were derived from in-depth case analyses and may differ from numbers of adverse events reported by investigators, as listed in Table 3.)

IMMUNOLOGIC INVESTIGATIONS

Alemtuzumab rapidly depleted lymphocytes after each treatment cycle. Lymphocyte reconstitution was similar for both doses. B-cell numbers returned to normal between 3 and 6 months. T-cell counts rose slowly and remained subnormal for the duration of the study; the median time for

Table 3. Adverse Events (Safety Population).*				
Adverse Event	Interferon Beta-1a (N=107)	Alemtuzumab		All Patients (N=216)
		12-mg Dose (N=108)	24-mg Dose (N=108)	
All events				
Any event				
Events — no. (no. per person-yr) [†]	1404 (5.3)	2229 (7.2)	2270 (7.2)	4499 (7.2)
Patients with event — no. (%)	107 (100.0)	108 (100.0)	107 (99.1)	215 (99.5)
Serious adverse event [‡]				
Events — no. (no. per person-yr)	87 (0.3)	43 (0.1)	73 (0.2)	116 (0.2)
Patients with event — no. (%)	24 (22.4)	24 (22.2)	27 (25.0)	51 (23.6)
Cancer [§]				
Events — no. (no. per person-yr)	1 (0.0036)	0 (0.0)	3 (0.0088)	3 (0.0044)
Patients with event — no. (%)	1 (0.9)	0 (0.0)	3 (2.8)	3 (1.4)
Death — no. (%)	0	1 (0.9)	1 (0.9)	2 (0.9)
Discontinuation because of adverse event — no. (%) [¶]	13 (12.1)	2 (1.9)	1 (0.9)	3 (1.4)
Infusion-associated reaction				
Any event — no. (%)		106 (98.1)	107 (99.1)	213 (98.6)
Serious adverse event — no. (%)		2 (1.9)	1 (0.9)	3 (1.4)
Infusion reaction		1 (0.9)	0 (0.0)	1 (0.5)
Abnormal liver-function test		0	1 (0.9)	1 (0.5)
Bradycardia		0	1 (0.9)	1 (0.5)
Hypertension		1 (0.9)	0	1 (0.5)
Events affecting >10% in any group — no. (%)				
Rash		96 (88.9)	102 (94.4)	198 (91.7)
Headache		60 (55.6)	72 (66.7)	132 (61.1)
Pyrexia		39 (36.1)	42 (38.9)	81 (37.5)
Fatigue		26 (24.1)	34 (31.5)	60 (27.8)
Pruritus		30 (27.8)	24 (22.2)	54 (25.0)
Nausea		22 (20.4)	30 (27.8)	52 (24.1)
Neurologic event		23 (21.3)	23 (21.3)	46 (21.3)
Chills		19 (17.6)	18 (16.7)	37 (17.1)
Insomnia		21 (19.4)	15 (13.9)	36 (16.7)
Chest discomfort		15 (13.9)	18 (16.7)	33 (15.3)
Dysgeusia		15 (13.9)	18 (16.7)	33 (15.3)
Dyspnea		14 (13.0)	14 (13.0)	28 (13.0)
Musculoskeletal discomfort		14 (13.0)	12 (11.1)	26 (12.0)
Dyspepsia		12 (11.1)	11 (10.2)	23 (10.6)
Vomiting		9 (8.3)	12 (11.1)	21 (9.7)
Flushing		11 (10.2)	9 (8.3)	20 (9.3)
Injection-site reaction				
Any — no. (%) ^{¶¶}	58 (54.2)	4 (3.7)	3 (2.8)	7 (3.2)

Table 3. (Continued.)				
Adverse Event	Interferon Beta-1a (N=107)	Alemtuzumab		All Patients (N=216)
		12-mg Dose (N=108)	24-mg Dose (N=108)	
Liver toxicity				
Any event — no. (%)				
Abnormal liver-function test ¶	16 (15.0)	2 (1.9)	3 (2.8)	5 (2.3)
Serious adverse event				
Hepatic failure	1 (0.9)	0	0	0
Abnormal liver-function test	1 (0.9)	0	2 (1.9)	2 (0.9)
Infection-associated event				
Any event — no. (%)†				
50 (46.7)	71 (65.7)	71 (65.7)	142 (65.7)	
Serious adverse event — no. (%)				
2 (1.9)	3 (2.8)	6 (5.6)	9 (4.2)	
Gastroenteritis	0	1 (0.9)	1 (0.9)	2 (0.9)
Bronchitis	0	0	1 (0.9)	1 (0.5)
Cellulitis	0	0	1 (0.9)	1 (0.5)
Cervicitis	0	1 (0.9)	0	1 (0.5)
Meningitis				
Listeria	0	0	1 (0.9)	1 (0.5)
Viral	0	0	1 (0.9)	1 (0.5)
Urinary tract infection	0	0	1 (0.9)	1 (0.5)
Varicella	0	1 (0.9)	0	1 (0.5)
Appendicitis	1 (0.9)	0	0	0
Central-venous-catheter infection	1 (0.9)	0	0	0
Events affecting >5% in any group — no. (%)				
Upper respiratory tract infection¶	29 (27.1)	48 (44.4)	55 (50.9)	103 (47.7)
Lower respiratory tract infection¶	2 (1.9)	12 (11.1)	15 (13.9)	27 (12.5)
Urinary tract infection	13 (12.1)	10 (9.3)	15 (13.9)	25 (11.6)
Herpes simplex virus infection	3 (2.8)	9 (8.3)	9 (8.3)	18 (8.3)
Influenza	6 (5.6)	10 (9.3)	4 (3.7)	14 (6.5)
Vaginitis	2 (1.9)	4 (3.7)	10 (9.3)	14 (6.5)
Herpes zoster	1 (0.9)	2 (1.9)	6 (5.6)	8 (3.7)
Autoimmune-associated event				
Thyroid-associated event — no. (%)				
Any event¶	3 (2.8)	28 (25.9)	21 (19.4)	49 (22.7)
Hyperthyroidism¶	1 (0.9)	17 (15.7)	15 (13.9)	32 (14.8)
Hypothyroidism**	1 (0.9)	8 (7.4)	7 (6.5)	15 (6.9)
Thyroiditis	1 (0.9)	6 (5.6)	3 (2.8)	9 (4.2)
Goiter	1 (0.9)	1 (0.9)	2 (1.9)	3 (1.4)
Thyroid cyst	0	1 (0.9)	0	1 (0.5)
Serious adverse event				
Hyperthyroidism	0	1 (0.9)	2 (1.9)	3 (1.4)

Table 3. (Continued.)

Adverse Event	Interferon Beta-1a (N=107)		Alemtuzumab	
		12-mg Dose (N=108)	24-mg Dose (N=108)	All Patients (N=216)
Immune thrombocytopenic purpura — no. (%)				
Any event	1 (0.9)	2 (1.9)	4 (3.7)	6 (2.8)
Serious adverse event	0	1 (0.9)	4 (3.7)	5 (2.3)
Other events affecting >10% of patients in any group				
General condition — no. (%)				
Fatigue	32 (29.9)	35 (32.4)	32 (29.6)	67 (31.0)
Pyrexia	11 (10.3)	12 (11.1)	12 (11.1)	24 (11.1)
Insomnia	16 (15.0)	15 (13.9)	10 (9.3)	25 (11.6)
Influenza-like illness¶	29 (27.1)	6 (5.6)	2 (1.9)	8 (3.7)
Weight increase	7 (6.5)	8 (7.4)	11 (10.2)	19 (8.8)
Contusion	3 (2.8)	4 (3.7)	12 (11.1)	16 (7.4)
Rash**	15 (14.0)	28 (25.9)	27 (25.0)	55 (25.5)
Neurologic symptom — no. (%)				
Neurologic event**	71 (66.4)	58 (53.7)	53 (49.1)	111 (51.4)
Headache	30 (28.0)	31 (28.7)	36 (33.3)	67 (31.0)
Dysgeusia†	22 (20.6)	10 (9.3)	7 (6.5)	17 (7.9)
Gastrointestinal condition — no. (%)				
Nausea	15 (14.0)	7 (6.5)	16 (14.8)	23 (10.6)
Diarrhea	7 (6.5)	10 (9.3)	15 (13.9)	25 (11.6)
Stomatitis**	2 (1.9)	5 (4.6)	13 (12.0)	18 (8.3)
Abdominal pain**	15 (14.0)	5 (4.6)	7 (6.5)	12 (5.6)
Musculoskeletal condition — no. (%)				
Discomfort	22 (20.6)	24 (22.2)	25 (23.1)	49 (22.7)
Pain in limb	14 (13.1)	17 (15.7)	23 (21.3)	40 (18.5)
Back pain	10 (9.3)	8 (7.4)	12 (11.1)	20 (9.3)
Arthralgia	11 (10.3)	15 (13.9)	9 (8.3)	24 (11.1)
Psychiatric condition — no. (%)				
Anxiety	12 (11.2)	10 (9.3)	13 (12.0)	23 (10.6)
Depression	19 (17.8)	14 (13.0)	17 (15.7)	31 (14.4)
Menstrual disorder in women — no. (%)	9 (12.9)	8 (11.4)	15 (21.7)	23 (16.5)

* All adverse events with onset after the first dose of a study drug through 36 months after the first dose are presented. Serious adverse events or autoimmune-associated events with an onset after the first dose through more than 36 months (through March 1, 2008) are presented. All P values are for the comparison between patients in both alemtuzumab groups and the interferon beta-1a group, except for infusion-associated reactions, in which the 12-mg dose of alemtuzumab is compared with the 24-mg dose. P values for the incidence of events were calculated with the use of Fisher's exact test; those for the rate of events are based on Poisson regression.

† P<0.01.

‡ Serious adverse events were defined as life-threatening, resulting in death, requiring or prolonging inpatient hospitalization, disabling, resulting in a congenital anomaly, or requiring medical or surgical intervention to prevent one of these outcomes. One patient contributed nearly half of the serious adverse events in the group receiving the 24-mg dose of alemtuzumab, and the majority of serious adverse events occurred after 36 months and related to exacerbations of conditions that predated the receipt of alemtuzumab. This patient received only one cycle of alemtuzumab, because her baseline EDSS score was retrospectively discovered to have exceeded the permitted maximum, and she was disqualified from further treatment. With the exception of this patient, serious adverse events were more than twice as frequent in patients receiving interferon beta-1a than in those receiving alemtuzumab and were largely due to hospitalizations for treatment of relapses of multiple sclerosis.

§ Cancers included colon cancer in a patient receiving interferon beta-1a and cervical cancer in situ, breast cancer, and non-EBV-associated Burkitt's lymphoma in patients receiving the 24-mg dose of alemtuzumab.

¶ P<0.001.

|| Infusion-associated reactions included any adverse event occurring during or within 2 days after alemtuzumab infusion.

** P<0.05.

recovery of CD4+ lymphocytes was 3 months for 100×10^6 cells per liter; the time ranged from 6 to 9 months for 200×10^6 cells per liter. Alemtuzumab-binding antibodies above the prespecified threshold of 2000 U per milliliter were detected in 1 of 208 patients (0.5%) and 51 of 194 patients (26.3%) at 12 and 24 months, respectively. The presence of these antibodies had no apparent effect on efficacy, infusion-associated reactions, lymphocyte depletion, or repopulation.

DISCUSSION

Among previously untreated patients with early, relapsing–remitting multiple sclerosis, alemtuzumab reduced the risk of sustained accumulation of disability by 71% and the risk of relapse by 74% ($P < 0.001$ for both), as compared with interferon beta-1a. Efficacy was maintained over 36 months, even though 72% of alemtuzumab-treated patients did not receive the planned third cycle of therapy at month 24 because of safety concerns. The reduction in the lesion load on T_2 -weighted MRI was greater among patients receiving alemtuzumab than among those receiving interferon beta-1a, although the difference at 36 months was not significant; comparisons were limited by missing MRI data and the high discontinuation rate for interferon beta-1a. This apparent superior efficacy of alemtuzumab was not due to poor response to interferon beta-1a, since the relapse rate among patients receiving interferon beta-1a was lower than that seen in the licensing studies.^{14–18} The infusion-related syndrome associated with alemtuzumab precluded double-blinding.¹⁹ Therefore, we used a rater who was unaware of treatment assignments for efficacy outcomes, as advocated by the American Academy of Neurology,²⁰ and confirmed successful maintenance of blinding throughout the study.

Although our study suggests that alemtuzumab is more effective than interferon beta-1a when given at the earliest stages of relapsing–remitting multiple sclerosis, our findings raise the difficult issue of exposing young adults who have little disability to a drug having potentially serious adverse effects. Our phase 2 trial was not designed to assess the long-term safety of alemtuzumab, nor was it powered to detect uncommon adverse events. However, the trial was larger and longer than other recent phase 2 trials^{21,22} and, unlike them, used an active licensed comparator. To date, the major safety concern is autoimmunity, already

known to be a generic complication of immune reconstitution from lymphocytopenia.^{23,24} Thyroid autoimmunity was observed, as reported previously.⁴

Immune thrombocytopenic purpura caused the death of one patient. After the report of two further cases, the data and safety monitoring board suspended the administration of alemtuzumab between September 2005 and May 2007. Risk minimization measures effectively identified subsequent patients with immune thrombocytopenic purpura, and such measures should be considered mandatory for the safe future use of alemtuzumab. Immune thrombocytopenic purpura was seen in 2.8% of patients receiving alemtuzumab and 0.9% of those receiving interferon beta-1a. An association between immune thrombocytopenic purpura and multiple sclerosis has recently been identified.^{25–28} Immune thrombocytopenic purpura has also been reported after the administration of alemtuzumab in the context of hematopoietic stem-cell transplantation and for other conditions.^{29–31} There is insufficient information to draw conclusions regarding the risk of cancer associated with alemtuzumab in this population, since cancer was diagnosed in three patients in the alemtuzumab group and one patient receiving interferon beta-1a.

Mean disability scores improved among patients in the alemtuzumab group, as first seen in our open-label study of alemtuzumab,² but worsened among those receiving interferon beta-1a. If improvements in disability after alemtuzumab are sustained, there would be important implications for the management of multiple sclerosis. An improvement of 0.39 EDSS point from a baseline score of 2.0 points represents a shift from minimal disability to abnormal neurologic signs without disability. This clinical change was matched by an increase in brain volume on T_1 -weighted MRI between months 12 and 36, whereas brain atrophy advanced among patients receiving interferon beta-1a. A possible mechanism may be the secretion of neurotrophins by lymphocytes that are regenerated after the administration of alemtuzumab.³² Together, these findings support the hypothesis that early suppression of inflammation in multiple sclerosis inhibits the complex cascade of disease mechanisms responsible for long-term disability.

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