Association Between Immediate Initiation of Intramuscular Interferon Beta-1a at the Time of a Clinically Isolated Syndrome and Long-term Outcomes

A 10-Year Follow-up of the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance

R. Philip Kinkel, MD; Mariya Dontchev, MPH; Craig Kollman, PhD; Thomai T. Skaramagas, BA; Paul W. O'Connor, MD; Jack H. Simon, MD, PhD; for the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance Investigators

Objective: To determine whether immediate initiation of treatment at the time of a clinically isolated syndrome in patients at high risk for clinically definite multiple sclerosis alters disease course over 10 years.

Design: Prospective follow-up study.

Setting: Twenty-four Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) sites in the United States and Canada.

Participants: A total of 81 patients originally randomly assigned to receive intramuscular interferon beta-1a (the immediate-treatment group) and 74 patients originally randomly assigned to receive placebo (the delayed-treatment group). All patients were from CHAMPS.

Intervention: For the immediate-treatment group, treatment was initiated within a month after the onset of a clinically isolated syndrome, and for the delayed-treatment group, treatment was initiated a median of 30 months (interquartile range, 24-35 months) after CHAMPS randomization.

Main Outcome Measures: Rate of developing clinically definite multiple sclerosis, annualized relapse rate, disease course classification, disability measures, and magnetic resonance imaging measures.

Results: The immediate-treatment group showed a lower 10-year rate of clinically definite multiple sclerosis (unadjusted hazard ratio, 0.64 [95% CI, 0.48-0.87]; $P=.004$) and a lower annualized relapse rate between years 5 and 10 ($P=.03$). There was no differential effect on disability, magnetic resonance imaging T2-weighted lesions, or the proportion of patients developing progressive disease at 10 years. Few patients reached the Expanded Disability Status Scale milestone scores of 4.0 or greater (9% of patients) or 6.0 or greater (6% of patients).

Conclusions: Immediate initiation of intramuscular interferon beta-1a at the time of a clinically isolated syndrome in high-risk patients reduces relapse rates over 10 years but does not improve disability outcomes compared with a control group that also initiated therapy relatively early in the disease course.

Trial Registration: clinicaltrials.gov Identifier: NCT00179478

Arch Neurol. 2012;69(2):183-190. Published online October 10, 2011. doi:10.1001/archneurol.2011.1426

Author Affiliations are listed at the end of this article.
Group Information: The Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance investigators are listed at the end of this article.

All interferon beta formulations and glatiramer acetate have been shown to delay the short-term risk of developing clinically definite multiple sclerosis (CDMS) in high-risk patients who had a clinically isolated syndrome (CIS).[1-4] Despite this consistent treatment effect, there is as yet no evidence that delaying the diagnosis of CDMS or decreasing relapse rates in this early, "at-risk" MS population improves long-term outcomes compared with delaying the initiation of therapy until patients demonstrate evidence of continued disease activity by clinical or magnetic resonance imaging (MRI) measures.[5,6]

CME available online at www.jamaarchivescme.com

To our knowledge, the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) was the first study to demonstrate the benefit of disease-modifying therapy in high-risk patients who had a CIS.[1] The Controlled

High-Risk Avonex Multiple Sclerosis Prevention Study In Ongoing Neurological Surveillance (CHAMPIONS) was conducted to determine whether patients in CHAMPS who initiated therapy with intramuscular interferon beta-1a (Avonex; Biogen Idec, Weston, Massachusetts) at the time of CIS onset (the immediate-treatment [IT] group) continued to experience treatment benefits compared with those who initiated treatment later (the delayed-treatment [DT] group).[5] The results of CHAMPIONS showed that the IT group experienced a lower rate of CDMS than did the DT group over 5 years, although very few patients in either group developed any significant disability. These 5-year results prompted us to continue CHAMPIONS for 10 years.

METHODS

PATIENTS

Patients participating in the original CHAMPIONS were eligible to continue in the 10-year extension if they provided informed consent and had no alternative neurologic diagnosis other than MS following enrollment in CHAMPS. The protocol and informed consent forms were approved by the institutional review board at each study site, and all patients gave written informed consent.

STUDY DESIGN

The entry criteria and protocol for CHAMPIONS have previously been described.[5] All patients at CHAMPS sites willing to participate were informed of the study results and given the opportunity to participate in CHAMPIONS without knowledge of their treatment assignment during CHAMPS. Patients originally randomly assigned to receive 30 µg of intramuscular interferon beta-1a once a week were characterized as the IT group, and those randomly assigned to receive placebo were characterized as the DT group. All patients were offered, but not required to take, 30 µg of intramuscular interferon beta-1a once a week at enrollment. All MS-related disease-modifying therapies and symptomatic therapies (with the exclusion of investigational therapies) were prescribed at the discretion of the study investigator and in accordance with local practices. The study protocol did not include the measurement of neutralizing antibodies against interferon beta.

During CHAMPIONS, it was decided to extend follow-up through 10 years from the original CHAMPS randomization. Study visits occurred annually with additional urgent visits to evaluate relapses.

STUDY OUTCOMES

The primary outcome measure in both CHAMPS and CHAMPIONS was the development of CDMS. This was determined by review of suspected cases by an independent blinded outcomes committee that maintained the same outcome definitions used in CHAMPS.

The following secondary outcomes in CHAMPIONS were determined at each annual visit by either the unmasked neurologist at the study site or a designee: number of relapses; disease course classification (relapsing active, stable and progressive active, or stable, based on status over previous year); and neurologic disability as measured by Expanded Disability Status Scale (EDSS)[7] and Multiple Sclerosis Functional Composite (MSFC) scores.[8] Patients were classified as progressive at the end of the study if they were progressive active at any study visit and did not revert to relapsing stable at any subsequent time point. The following secondary outcomes were determined by the central MRI reading center (masked to previous/current treatment): number of new or enlarging T2-weighted lesions, change in T2-weighted lesion volume from CHAMPS baseline to 10 years, and number of gadolinium-enhancing lesions at 10 years. Serious adverse events were monitored throughout the study.

STATISTICAL METHODS

Statistical analysis of CHAMPIONS data was conducted as in the CHAMPS trial, as appropriate. Two-sided tests of significance were used; all analyses were conducted as intention-to-treat, with no correction for time on or off treatment. Kaplan-Meier rates for the development of CDMS were calculated using timing from the first month. Analysis of CDMS in combination with MRI-detected lesions included patients with 10-year MRI data. Analysis of CDMS included all 383 patients originally randomly assigned in CHAMPS. Patients who did not meet the criteria for CDMS were censored on the date of the last neurologic evaluation (during either CHAMPS or CHAMPIONS). Unadjusted and adjusted hazard ratios were determined from a proportional hazards model. A multivariate model was adjusted for age, presenting event, number of baseline brain MRI T2-weighted lesions, and number of gadolinium-enhancing lesions at baseline. The effect modification related to these factors was assessed with interaction terms in the model. Possible violations of the proportional hazards assumption were checked using time-dependent variables. Other outcomes were compared between the IT and DT groups using the Fisher exact test or the Wilcoxon rank sum test as indicated. Analyses of disease course, EDSS scores, and MSFC scores were limited to patients who completed the 10-year evaluation. To accommodate an initial patient learning curve, reference values obtained after the 5-year visit were used only when the 5-year visit was the first time an MSFC test was administered. The MSFC *z* scores were calculated using the 5-year value (for 113 patients) or the value obtained during the next examination (for 2 patients at their 5.5-year visit, 11 patients at their 6-year visit, and 1 patient at his or her 7-year visit) as the reference value. Because of the large number of statistical comparisons performed in the analysis, *P* values of .01 or greater were not considered statistically significant for secondary outcomes.

RESULTS

ACCOUNTING OF PATIENTS AND TREATMENTS

Figure 1 provides an accounting of patients from CHAMPS through the 10-year extension study. An equal distribution of patients from the original CHAMPS interferon beta-1a (n=100) and placebo (n=103) groups enrolled in the CHAMPIONS 5-year extension, but a slightly higher number of patients from the IT group enrolled in the 10-year extension (81 patients for IT group vs 74 patients for DT group). Reasons for not participating in the 10-year extension included the following: the patient was lost to follow-up (n=13), moved (n=4), refused to participate (n=5), was deceased (n=1), was participating in another study (n=1), or no reason was given (n=4). The 28 CHAMPIONS patients at the 24 eligible sites who did not participate in the 10-year extension were predominately from the original CHAMPIONS DT group (19 patients [68%]) and had a higher rate of conversion to CDMS at 5 years (16 patients [57%]) than did the 155

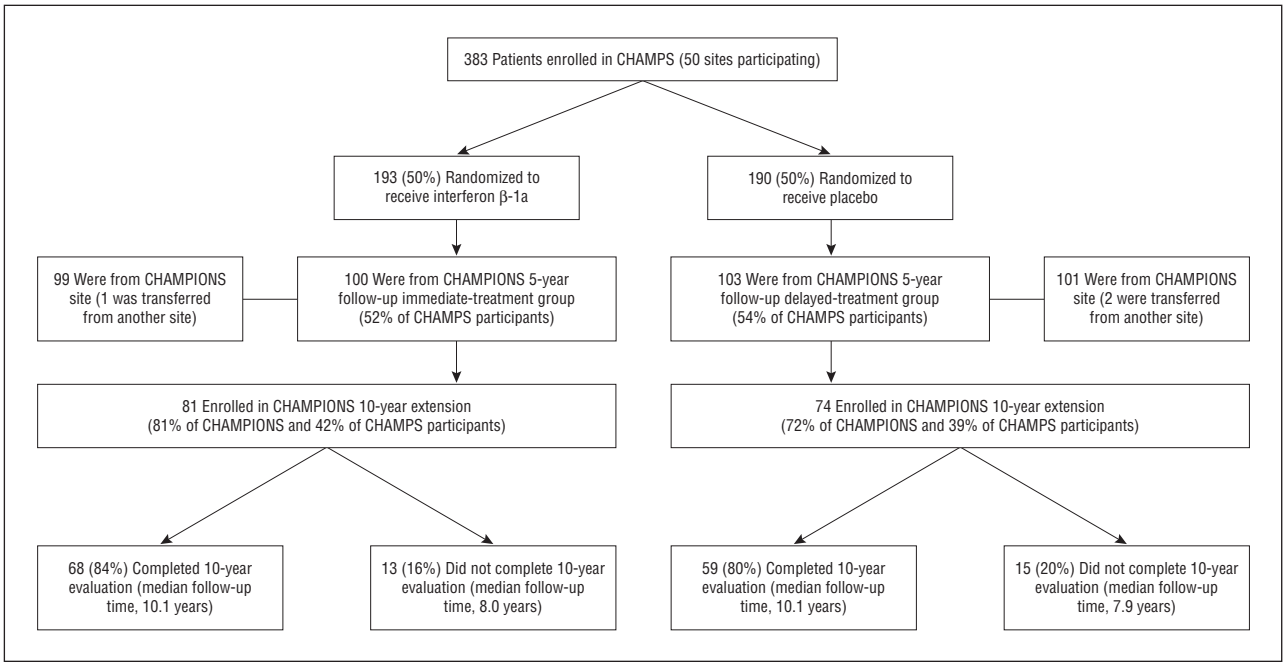


Figure 1. Progression from the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) through the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance (CHAMPIONS). Thirty-two of the 50 CHAMPS sites participated in the CHAMPIONS 5-year follow-up (a total of 293 CHAMPS patients at these 32 sites). Twenty-four of the 32 CHAMPIONS 5-year follow-up sites participated in the CHAMPIONS 10-year extension (a total of 183 CHAMPS patients at these 24 sites). The percentages in the bottom row of boxes are based on the participants enrolled in the 10-year extension. The percentage among all CHAMPS participants who completed the 10-year evaluation was 35% in the immediate-treatment group and 31% in the delayed-treatment group. The median follow-up time for all subjects participating in the 10-year extension was 10.0 years.

Table 1. Baseline Demographic and Clinical Characteristics of Patients in CHAMPIONS 10-Year Follow-up at Onset of CHAMPS

Characteristic	Patients, No. (%)		
	Total[a] (n=155)	Immediate Treatment (n=81)	Delayed Treatment (n=74)
Age, mean (SD), y	34 (7)	35 (7)	34 (7)
White	141 (91)	72 (89)	69 (93)
Female	113 (73)	60 (74)	53 (72)
Family history of MS	15 (10)	10 (12)	5 (7)
Presenting event			
Brainstem-cerebellar syndrome	40 (26)	21 (26)	19 (26)
Optic neuritis	78 (50)	40 (49)	38 (51)
Spinal cord disease	37 (24)	20 (25)	17 (23)
EDSS score[b]			
≤1.5	102 (66)	47 (58)	55 (74)
2.0-2.5	39 (25)	24 (30)	15 (20)
≥3.0	14 (9)	10 (12)	4 (5)
No. of MRI T2-weighted lesions[c]			
2-8	40 (26)	22 (28)	18 (25)
9-13	49 (32)	25 (31)	24 (33)
14-23	31 (20)	14 (18)	17 (23)
≥24	33 (22)	19 (24)	14 (19)
Median (IQR)	13 (8-21)	13 (8-22)	13 (9-20)
MRI T2-weighted lesion volume,[d] mm^3, median (IQR)	1930 (918-4945)	2063 (1003-4945)	1774 (786-4883)
No. of gadolinium-enhancing lesions[e]			
0	105 (71)	50 (66)	55 (76)
1	21 (14)	13 (17)	8 (11)
≥2	22 (15)	13 (17)	9 (13)

Abbreviations: CHAMPIONS, Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance; CHAMPS, Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study; EDSS, Expanded Disability Status Scale; IQR, interquartile range; MRI, magnetic resonance imaging; MS, multiple sclerosis.

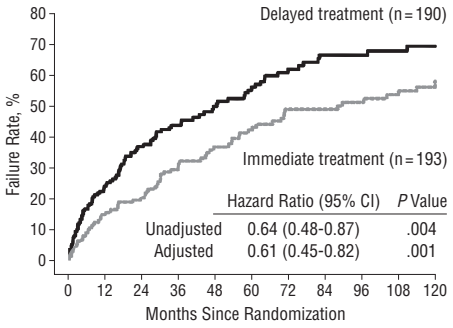
[a] There were 383 patients in CHAMPS.

[b] After 1 month in CHAMPS.

[c] Baseline number of MRI T2-weighted lesions is missing for 2 patients.

[d] Baseline MRI T2-weighted volume is missing for 6 patients.

[e] Baseline number of gadolinium-enhancing lesions is missing for 7 patients.



Delayed treatment											
No. of patients at interval start	190	133	94	65	58	48	35	26	26	24	10
No. of CDMS cases during interval	42	23	10	7	6	6	5	0	1	1	0
No. of patients censored during interval	15	16	19	0	4	7	4	0	1	13	10
CDMS failure rate, %	4	23	37	44	50	55	61	66	66	68	69
Immediate treatment											
No. of patients at interval start	193	146	112	78	69	63	53	48	40	38	22
No. of CDMS cases during interval	27	9	12	8	6	7	0	2	2	2	1
No. of patients censored during interval	20	25	22	1	0	3	5	6	0	14	21
CDMS failure rate, %	2	15	20	30	37	42	49	49	51	54	58

Figure 2. Kaplan-Meier rates for the development of clinically definite multiple sclerosis (CDMS) by treatment group, calculated using timing from the first month. Data include all patients (n = 383) originally randomly assigned to the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study. Patients not meeting the criteria for CDMS were censored on the date of their last neurologic examination.

patients who did participate (70 patients [45%]). The baseline characteristics of the 155 patients participating in the 10-year extension are shown in **Table 1**.

The median time to initiation of treatment with interferon beta-1a in the DT group was 30 months (interquartile range, 24-35 months) after CHAMPS randomization. Thirty-four percent of DT patients started treatment after the development of CDMS, and 81% of the DT group developed CDMS or 1 or more new or enlarging T2-weighted lesion within 18 months of being randomly assigned in the original CHAMPS and while still receiving placebo.

At 5 years, 31 of 81 patients (38%) in the IT group and 39 of 74 (53%) in the DT group developed CDMS. Of the 155 patients who enrolled in the 10-year extension, 127 (82%) completed their 10-year evaluation (Figure 1), and 110 (71%) had an MRI scan at that visit.

The use of interferon beta-1a was similar in the IT and DT groups. At the 5-year visit, 130 of the 155 patients (84%) (ie, 66 of 81 patients in the IT group [81%] vs 64 of 74 patients in the DT group [86%]) were receiving only intramuscular interferon beta-1a. By the last study visit, 88 of the 155 patients (57%) (ie, 45 of 81 patients in the IT group [56%] vs 43 of 74 patients in the DT group [58%]) were receiving intramuscular interferon beta-1a (with 2 patients in the IT group also receiving an alternative therapy), 19 of the 155 patients (12%) (ie, 6 of 81 patients in the IT group [7%] vs 13 of 74 patients in the DT group [18%]) were receiving an alternative therapy without interferon beta-1a, and 46 of the 155 patients (30%) (28 of 81 patients in the IT group [35%] vs 18 of 74 patients in the DT group [24%]) were receiving no therapy. Alternative therapies included subcutaneous interferon beta-1b and interferon beta-1a, glatiramer acetate, intervals of high-dose corticosteroid treatment, mitoxantrone hydrochloride, and natalizumab.

PRIMARY OUTCOME

At 10 years, the cumulative probability of developing CDMS was significantly lower in the IT group (58% [95% CI, 48%-68%]) than in the DT group (69% [95% CI, 61%-78%]) (unadjusted hazard ratio 0.64 [95% CI, 0.48-0.87]; $P = .004$) (**Figure 2**). The treatment effect was comparable when adjusting for age, CHAMPS qualifying event, number of CHAMPS baseline brain MRI T2-weighted lesions, and baseline number of gadolinium-enhancing lesions (adjusted hazard ratio, 0.61 [95% CI, 0.45-0.82]; $P = .001$). In this Cox proportional hazards model, a younger age at onset, 9 or more T2-weighted lesions at baseline, and 2 or more gadolinium-enhancing lesions at baseline were all independently associated with a higher rate of CDMS over 10 years (**Table 2**). Similar primary outcome results were obtained when only those patients participating in the 10-year extension were analyzed (data not shown).

ANNUALIZED RELAPSE RATES

The annualized relapse rate in the DT group was double that of the IT group from years 5 to 10 (0.31 vs 0.14; $P = .03$) (**Table 3**), even though use of interferon beta-1a was comparable during that time. A similar trend was observed during the first 5 years (0.36 vs 0.18) and over the entire 10 years (0.33 vs 0.16), but these differences did not meet the 0.01 threshold for statistical significance. Annualized relapse rates remained lower in the IT group between years 5 and 10 when only those patients who developed CDMS by 5 years were included in the analysis (0.45 vs 0.24; $P = .16$), although this did not reach statistical significance. Between years 5 and 10, the IT group was more likely than the DT group to experience no relapses (40 of 68 patients [59%] in the IT group vs 25 of 59 patients [42%] in the DT group), and the DT group was more likely than the IT group to experience 3 or more relapses (15 of 59 patients [25%] in the DT group vs 6 of 68 patients [9%] in the IT group). Over the entire period of observation, 31% of patients experienced no relapses.

ADDITIONAL CLINICAL OUTCOMES AT 10 YEARS

Of 127 patients who completed the 10-year evaluation, 117 (92%) still had a relapsing disease at 10 years (**Table 4**). At 10 years, 81% of patients had EDSS scores of less than 3.0; 9% of all patients and 16% of CDMS patients reached an EDSS score of 4.0 or greater, and 6% of all patients and 10% of CDMS patients reached an EDSS score of 6.0 or greater. The MSFC z scores showed no

Table 2. Cox Regression Multivariate Model for Outcome of Clinically Definite Multiple Sclerosis[a]

Factor	Patients, No.	Adjusted HR (95% CI)[b]	*P* Value	Favorable
IT group	193	0.61 (0.45-0.82)	.001	IT group
Age (per decade)	NA	0.61 (0.49-0.75)	<.001	Older
Presenting event				
Spinal cord disease	83	1 [Reference]		
Optic neuritis	192	1.25 (0.85-1.84)	.25	
Brainstem-cerebellar syndrome	108	0.93 (0.60-1.42)	.72	
No. of MRI T2-weighted lesions at baseline[c]				Fewer MRI T2-weighted lesions
2-8	90	1 [Reference]		
9-13	101	1.75 (1.09-2.82)	.02	
14-23	97	2.29 (1.41-3.69)	<.001	
≥24	89	2.67 (1.66-4.31)	<.001	
≥2 Gadolinium-enhancing lesions at baseline[d]	51	1.89 (1.26-2.83)	.002	≤1 Gadolinium-enhancing lesion

Abbreviations: HR, hazard ratio; IT, immediate treatment; MRI, magnetic resonance imaging; NA, not applicable.
[a] Includes all 383 patients originally randomly assigned to the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study. Patients not meeting the criteria for clinically definite multiple sclerosis were censored on the date of their last neurologic examination. $P<.01$ was considered to be statistically significant.
[b] Adjusted for all other factors in the table.
[c] Missing baseline number of MRI T2-weighted lesions (6 patients) was treated as a separate category in the model (data not shown).
[d] Missing baseline number of gadolinium-enhancing lesions (21 patients) was treated as a separate category in the model (data not shown).

Table 3. Relapse Rates for Patients in CHAMPIONS 10-Year Follow-up

	Mean (SD)			
Relapse Rate	Total[a] (n=127)	Immediate Treatment (n=68)	Delayed Treatment (n=59)	*P* Value[b]
Annual relapse rates by epoch				
Years 0-2	0.25 (0.44)	0.15 (0.30)	0.36 (0.54)	.009
Years 0-5	0.26 (0.44)	0.18 (0.23)	0.36 (0.58)	.04
Years 5-10	0.22 (0.33)	0.14 (0.21)	0.31 (0.41)	.03
Years 0-10	0.24 (0.32)	0.16 (0.18)	0.33 (0.41)	.02
Relapse free, 0-10 years, No. (%)	40 (31)	24 (35)	16 (27)	.34

Abbreviation: CHAMPIONS, Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance.
[a] Limited to 127 of 155 patients who completed the 10-year evaluation. Results were similar using last observation carried forward for the 28 subjects who did not complete the 10-year evaluation (data not shown).
[b] Determined by use of the Wilcoxon rank sum test. Because of multiple comparisons, $P\geq.01$ was considered not to be significant in secondary analyses.

overall worsening compared with 5-year values (median, 0.09). No significant differences were seen between the IT and DT groups on these outcomes (Table 4). Similar results were obtained when the last examination score was carried forward for the 28 patients who did not complete their 10-year evaluation (data not shown).

MRI OUTCOMES AT 10 YEARS

There were no significant differences between the IT and DT groups for any of the MRI measures (**Table 5**). On average, T2-weighted lesion volume more than doubled from the CHAMPS baseline to 10 years (median change, 120% or 2539 mm^3), although these percentage increases partially reflect the low T2-weighted lesion volumes at the onset of CHAMPS. Using a combined outcome measure of MRI with CDMS events, we found that 96% (ie, the Kaplan-Meier rate [95% CI, 92%-100%]) of patients developed CDMS and/or 1 or more new or enlarging T2-weighted lesions by 10 years and that 91% (95% CI, 84%-98%) of patients developed CDMS and/or 2 or more new or enlarging T2-weighted lesions by 10 years. Only 4 of 61 patients with CDMS (7%) and 8 of 49 patients without CDMS (16%) remained free of new or enlarging T2-weighted lesions.

SAFETY

Over the entire CHAMPIONS follow-up (both the 5- and 10-year extensions), there were 34 serious adverse events in 25 patients, including 2 deaths (metastatic breast cancer and an automobile accident). There was no difference by treatment group (16 patients in the IT group and 18 patients in the DT group had serious adverse events). Unmasked investigators considered all serious adverse events unrelated or unlikely to be related to the study drug. No new safety concerns with interferon beta-1a therapy were identified.

COMMENT

The CHAMPIONS 10-year extension follow-up confirms and extends the results of the phase 3 CHAMPS and the 5-year CHAMPIONS.[1,5] Patients at high risk for

Table 4. Disease Type and Disability at 10 Years

10-Year Outcome	Patients, No. (%)			*P* Value[b]
	Total[a] (n=127)	Immediate Treatment (n=68)	Delayed Treatment (n=59)	
Disease course				
Relapsing	117 (92)	61 (90)	56 (95)	.34
Progressive	10 (8)	7 (10)	3 (5)	
EDSS score				
0.0-2.5	103 (81)	56 (82)	47 (80)	.61
3.0-3.5	12 (9)	5 (7)	7 (12)	
4.0-5.5	5 (4)	2 (3)	3 (5)	
≥6.0	7 (6)	5 (7)	2 (3)	
MSFC				
Composite *z* score,[c] median (IQR)	0.09 (–0.31 to 0.49)	0.13 (–0.32 to 0.52)	–0.06 (–0.30 to 0.45)	.51
>20% worsening in 25-FW time from 5 to 10 y	22 (18)	12 (18)	10 (18)	.99
>20% worsening in 9-HPT scores from 5 to 10 y	6 (5)	4 (6)	2 (3)	.69

Abbreviations: EDSS, Expanded Disability Status Scale; IQR, interquartile range; MSFC, Multiple Sclerosis Functional Composite; 9-HPT, 9-Hole Peg Test; 25-FW, 25-Foot Walk Test.

[a] Limited to 127 of 155 patients who completed the 10-year evaluation. Results were similar using the last observation carried forward for the 28 subjects who did not complete the 10-year evaluation (data not shown).

[b] Determined by use of the Fisher exact test. Because of multiple comparisons, $P \geq .01$ was considered not to be significant in secondary analyses.

[c] The MSFC 10-year value is missing for 3 patients. Change from 5 to 10 years analyzed for 124 patients with data available at both time points. The MSFC *z* scores were calculated using mean and standard deviation values from the 5-year visit; for patients whose first MSFC score was obtained at 5 years, the value from the next completed visit was used. The composite *z* score was taken as the average of the 25-FW, 9-HPT, and Paced Auditory Serial Addition Test scores. A higher *z* score denotes a favorable outcome.

Table 5. Magnetic Resonance Imaging Findings at 10 Years

10-Year MRI Measure[a]	Patients, No. (%)			*P* Value[b]
	Total (n=110)	Immediate Treatment (n=55)	Delayed Treatment (n=55)	
No. of new or enlarging T2-weighted lesions				
0-2	28 (25)	17 (31)	11 (20)	.50
3-6	31 (28)	16 (29)	15 (27)	
7-14	24 (22)	11 (20)	13 (24)	
≥15	27 (25)	11 (20)	16 (29)	
Median (IQR)	6 (2-4)	5 (1-12)	7 (3-17)	
No. of gadolinium-enhancing lesions[c]				
0	87 (81)	44 (81)	43 (80)	.87
1	14 (13)	6 (11)	8 (15)	
≥2	7 (6)	4 (7)	3 (6)	
T2-weighted lesion volume at 10 y, median (IQR), mm^3	4826 (2089-11 611)	4741 (1906-11 902)	4946 (2089-11 611)	.79
Change in T2 volume,[d] median (IQR), mm^3				
Change from baseline to 5 y	561 (–51 to 2480)	311 (–167 to 2125)	775 (170-2710)	.07
Change from 5 to 10 y	1358 (370-3592)	1752 (460-4621)	917 (199-3060)	.26
Change from baseline to 10 y	2539 (594-6503)	2600 (398-5862)	2516 (721-6682)	.64

Abbreviations: IQR, interquartile range; MRI, magnetic resonance imaging.

[a] Limited to 110 of 155 patients who completed the 10-year evaluation. This measure excludes 17 patients who completed the 10-year evaluation but did not have an MRI scan available for analysis. There were no significant differences between the immediate-treat and delayed-treatment groups.

[b] Determined by use of the Wilcoxon rank sum test for the T2-weighted lesion volume and change and for the percentage change in T2-weighted lesion volume, and by use of the Fisher exact test for the number of T2-weighted lesions and gadolinium-enhancing groups. Because of multiple comparisons, $P \geq .01$ was considered not to be significant in secondary analyses.

[c] Missing for 2 MRI scans.

[d] For 100 patients with T2-weighted lesion volume available at both baseline and 5 years, 102 patients with T2-weighted lesion volume available at both 5 and 10 years, and 108 patients with T2-weighted lesion volume available at both baseline and 10 years.

MS who initiated therapy with intramuscular interferon beta-1a immediately after onset of a CIS developed CDMS at a lower rate over 10 years and experienced lower annualized relapse rates during all treatment periods than patients who initiated intramuscular interferon beta-1a therapy a median of 2.5 years after CIS onset. Overall, annualized relapse rates were low in both groups, and there was no difference in standard MRI outcomes at either 5 or 10 years. These results suggest that immediate initiation of intramuscular interferon beta-1a in high-risk patients who had a CIS delays the development of CDMS but has only a modest effect on subsequent relapses and no significant effect on new MRI T2-weighted lesions (ie, inflammatory activity) compared with a randomized group

that delayed the onset of therapy until most patients (at least 81%) had experienced either a second CDMS-defining relapse or the development of a new or enlarging T2-weighted lesion identified on an MRI scan.

Few patients in the IT or DT groups developed significant disability (defined as an EDSS score of ≥4.0 [9% of all patients] or ≥6.0 [6% of all patients]) by their last visit, and no difference in disability outcomes between the IT and DT groups was indicated by either the EDSS or MSFC scores. Similarly, the Betaseron in Newly Emerging MS for Initial Treatment (BENEFIT) trial reported no differential effect on disability outcomes 5 years after CIS onset despite a continued reduction in the rate of development of CDMS.[6] There are many potential reasons for the disparity between the relapse and disability outcomes in early CIS trials. These include relatively early treatment in all CIS follow-up groups, selective attrition of patients with highest relapse activity, and a relative minority of patients with enough early relapses to drive the development of early disability. Selective attrition of the CHAMPIONS patients, at least at 5 years, is an unlikely explanation given the nearly identical results reported by the BENEFIT 5-year investigators with a high rate of study completion.[6] With observation periods as long as 10 years, one must consider the possibility of a limited association between relapses (particularly after 5 years of disease) and the development of disability. The lack of association between relapses beyond the first 5 years of MS and subsequent disability has been reported in recent natural history studies.[9]

Evidence from the long-term follow-up of more established relapsing-remitting patients who participated in clinical trials of interferon beta therapy or in long-term observational studies suggest that similar delays in therapy may have a larger effect on long-term disability outcomes.[10,11] In fact, the evidence from multiple clinical trials involving both patients with relapsing-remitting MS and patients with secondary progressive MS suggests that there is a window of opportunity for the initiation of effective disease-modifying therapy beyond which initiating treatment has diminishing effects on the development of disability.[12] Consideration of the data from long-term follow-up of CIS trials suggests that, for patients originally randomly assigned to receive placebo, treatment with disease-modifying therapy initiated at the time of a second attack or up to 2.5 years after symptom onset was within this window of opportunity. These follow-up results provide further evidence of clinical equipoise in the design of future CIS trials that involve placebo controls.

The CHAMPIONS 10-year follow-up results suggest that early treatment for high-risk patients who had a CIS may positively alter the natural history of MS. Because IT and DT groups experienced similar disability outcomes at 10 years and because 31% of patients experienced no relapses over 10 years, further studies are required to determine whether there are particular high-risk groups that require immediate initiation of disease-modifying therapy. Because the majority of patients began therapy after the development of a second CDMS-defining attack or after the development of new MRI-detected lesions, strong consideration should be given to the initiation of therapy when these conditions are met. The present study results are in agreement with previous reports[13,14] showing an extremely low rate of severe, residual disability after an MS relapse and, in particular, after a second clinical attack. These results suggest that monitoring select patients (perhaps those with <9 MRI T2-weighted lesions at onset and no asymptomatic gadolinium-enhancing lesions) with serial MRI before initiating therapy may be an option until better biomarkers of disease activity are available to guide treatment decisions.[15,16]

We acknowledge the limitations of our long-term study design, particularly the possibility of selective attrition of patients with greater levels of disease activity. Although only 40% of the original CHAMP patients enrolled in our 10-year extension study, there is good evidence that the 10-year participants are reflective of the original 5-year CHAMPIONS patients. In the final analysis, the CHAMPIONS 10-year cohort reflects a sampling of the CHAMPIONS 5-year cohort, which in turn was only a sampling of the original CHAMPS cohort. As with all sampling, there is a possibility of significant nonrandom differences between cohorts. For future phase 3 studies of CIS trials, we suggest the development of guidelines to encourage and facilitate long-term follow-up, including tracking and contacting consenting patients by use of a central data management center; incorporating a predetermined, registered statistical management plan for long-term follow-up into the original trial design; and using different measures to maximize study subject and site retention.

Accepted for Publication: August 3, 2011.
Published Online: October 10, 2011. doi:10.1001/archneurol.2011.1426
Author Affiliations: Multiple Sclerosis Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts (Dr Kinkel); Jaeb Center for Health Research, Tampa, Florida (Ms Dontchev and Dr Kollman); Cleveland Clinic Foundation, Ohio (Ms Skaramagas); St Michael's Hospital, Toronto, Ontario, Canada (Dr O'Connor); and Portland Veterans Affairs Medical Center, Oregon (Dr Simon).
Correspondence: R. Philip Kinkel, MD, Multiple Sclerosis Center, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, KS 211, Boston, MA 02215 (rkinkel@bidmc.harvard.edu).
Author Contributions: *Study concept and design:* Kinkel, O'Connor, and Simon. *Acquisition of data:* Kinkel, Kollman, Skaramagas, O'Connor, and Simon. *Analysis and interpretation of data:* Kinkel, Dontchev, Kollman, O'Connor, and Simon. *Drafting of the manuscript:* Kinkel, Dontchev, O'Connor, and Simon. *Critical revision of the manuscript for important intellectual content:* Kinkel, Kollman, Skaramagas, O'Connor, and Simon. *Statistical analysis:* Kinkel, Dontchev, and Kollman. *Obtained funding:* Kinkel. *Administrative, technical, and material support:* Kinkel, Skaramagas, and Simon. *Study supervision:* Kinkel and Kollman.
CHAMPIONS Investigators: Douglas Arnold, MD, Montreal Neurological Institute, Quebec, Canada; Staley Brod, MD, University of Texas Health Science Center at Houston; Pierre Duquette, MD, Hospital Notre Dame, Montreal, Quebec, Canada; Eric Eggenberger, MD, Michigan State University, East Lansing; Warren Felton, MD, Virginia Commonwealth University, Richmond; Robert Fox,

MD, Cleveland Clinic Foundation, Ohio; Mark Freedman, MD, Ottawa General Hospital, Ontario, Canada; Steven Galetta, MD, University of Pennsylvania Medical Center, Philadelphia; Andrew Goodman, MD, University of Rochester, New York; Joseph Guarnaccia, MD, MS Treatment Center, Griffin Hospital, Derby, CT; Stanley Hashimoto, MD, University of British Columbia, Vancouver, Canada; Michael Kaufman, MD, Carolinas Medical Center, Charlotte, NC; Lawrence Kerson, MD, The Neurology Group, Norristown, PA; Thomas Murray, MD, Queen Elizabeth II Health Sciences Centre, Centre for Clinical Research, Halifax, Nova Scotia, Canada; Paul W. O'Connor, MD, University of Toronto, Ontario, Canada; Kottil Rammohan, MD, Ohio State University, Columbus; Merrell Reiss, MD, Beta Research, Inc, Westmont, IL; Loren Rolak, MD, Marshfield Clinic, Wisconsin; Thomas Scott, MD, Allegheny Neurological Associates, Pittsburgh, PA; John Selhorst, MD, St Louis University, Missouri; William Stuart, MD, MS Center of Atlanta, Georgia; Stephen Thurston, MD, Neurological Associates, Inc, Richmond, VA; Michael Wall, MD, University of Iowa, Iowa City; Bianca Weinstock-Guttman, MD, Buffalo General Hospital, Jacobs Neurological Institute, New York.

Financial Disclosure: Dr Kinkel has received either personal compensation or financial support from his institution for activities in collaboration with pharmaceutical companies (including Acorda, Avanir, Biogen Idec, and Teva) that develop products for MS. He has also received grant support from the National MS Society as well as support as section editor of *Reviews in Neurological Diseases*. Dr O'Connor has received either personal compensation or financial support from his institution for activities in collaboration with pharmaceutical companies (including Actelion, Biogen Idec, Celgene, sanofi-aventis, EMD Serono, Abbott, Teva, Bayer, BioMS Technology Corp, Genentech, Lilly, Roche, and Novartis) that develop products for MS. He has received grant support from the MS Society of Canada and Direct-MS. Dr Simon has received either personal compensation or financial support from his institution for activities related to pharmaceutical companies (including Genzyme, Protein Design Labs, Pfizer, Genentech, Bristol-Myers Squibb, Artielle Immunotherapeutics, BioMS Technology Corp, and Biogen Idec) that develop products for MS.
Funding/Support: This study was funded by Biogen Idec.

REFERENCES

1. Jacobs LD, Beck RW, Simon JH, et al; CHAMPS Study Group. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med*. 2000;343(13):898-904.
2. Comi G, Filippi M, Barkhof F, et al; Early Treatment of Multiple Sclerosis Study Group. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet*. 2001;357(9268):1576-1582.
3. Comi G, Martinelli V, Rodegher M, et al; PreCISe study group. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;374(9700):1503-1511.
4. Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology*. 2006;67(7):1242-1249.
5. Kinkel RP, Kollman C, O'Connor P, et al; CHAMPIONS Study Group. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. *Neurology*. 2006;66(5):678-684.
6. Kappos L, Freedman MS, Polman CH, et al; BENEFIT Study Group. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. *Lancet Neurol*. 2009;8(11):987-997.
7. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-1452.
8. Rudick RA, Cutter G, Reingold S. The multiple sclerosis functional composite: a new clinical outcome measure for multiple sclerosis trials. *Mult Scler*. 2002; 8(5):359-365.
9. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y; UBC Neurologists. Impact of multiple sclerosis relapses on progression diminishes with time. *Neurology*. 2009;73(20):1616-1623.
10. Kappos L, Traboulsee A, Constantinescu C, et al. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. *Neurology*. 2006; 67(6):944-953.
11. Trojano M, Pellegrini F, Paolicelli D, et al; Italian Multiple Sclerosis Database Network (MSDN) Group. Real-life impact of early interferon beta therapy in relapsing multiple sclerosis. *Ann Neurol*. 2009;66(4):513-520.
12. Cohen JA, Antel JP. Does interferon beta help in secondary progressive MS? *Neurology*. 2004;63(10):1768-1769.
13. Bejaoui K, Rolak LA. What is the risk of permanent disability from a multiple sclerosis relapse? *Neurology*. 2010;74(11):900-902.
14. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. *Neurology*. 2003;61(11):1528-1532.
15. CHAMPS Study Group. Predictors of short-term disease activity following a first clinical demyelinating event: analysis of the CHAMPS placebo group. *Mult Scler*. 2002;8(5):405-409.
16. CHAMPS Study Group. MRI predictors of early conversion to clinically definite MS in the CHAMPS placebo group. *Neurology*. 2002;59(7):998-1005.