


Matching comparisons of therapeutic efficacy suggest better clinical outcomes for patients treated with peginterferon beta-1a than with glatiramer acetate

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Abstract

Background: Peginterferon beta-1a and glatiramer acetate (GA) are approved first-line therapies for the treatment of relapsing forms of multiple sclerosis, but their therapeutic efficacy has not been compared directly.

Methods: Clinical outcomes at 2 years, including no evidence of disease activity (NEDA), for patients receiving peginterferon beta-1a 125 mcg every 2 weeks (Q2W) or GA 20 mg/ml once daily (QD) were compared by propensity score matching analysis using individual patient data from ADVANCE and CONFIRM phase III clinical trials. In addition, clinical outcomes at 1–3 years for patients receiving peginterferon beta-1a Q2W or GA 40 mg/ml three times a week (TIW) were evaluated using a matching-adjusted comparison analysis of individual patient data from ADVANCE and the ADVANCE extension study, ATTAIN, and aggregate patient data from the phase III GALA and the GALA extension studies.

Results: Propensity-score-matched peginterferon beta-1a patients ($n=336$) had a significantly lower annualized relapse rate [ARR (0.204 versus 0.282); rate ratio=0.724; $p=0.045$], a significantly lower probability of 12-week confirmed disability worsening (10.0% versus 14.6%; hazard ratio=0.625; $p=0.048$), and a significantly higher rate of NEDA (20.3% versus 11.5%; $p=0.047$) compared with GA 20 mg/ml QD patients after 2 years of treatment. Matching-adjusted peginterferon beta-1a patients (effective $n=276$) demonstrated a similar ARR at 1 year (0.278 versus 0.318; $p=0.375$) and significantly lower ARR at 2 years (0.0901 versus 0.203; $p=0.032$) and 3 years (0.109 versus 0.209; $p=0.047$) compared with GA 40 mg/ml TIW patients ($n=834$).

Conclusion: Results from separate matching comparisons of phase III clinical trials and extension studies suggest that peginterferon beta-1a 125 mcg Q2W may provide better clinical outcomes than GA (20 mg/ml QD or 40 mg/ml TIW).

Keywords: comparative efficacy, glatiramer acetate, multiple sclerosis, peginterferon beta-1a

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Introduction

Multiple sclerosis is a heterogeneous disease, and patients can present with varying degrees of disease activity at initial diagnosis. Current practice guidelines recommend that health care providers (HCPs) consider the risks and benefits of each treatment strategy on a patient-by-patient basis.^{1,2} Peginterferon beta-1a and glatiramer acetate (GA)

are both approved first-line therapies for the treatment of relapsing forms of multiple sclerosis.^{3,4} However, their therapeutic efficacy has not been compared directly in head-to-head studies.

In the phase III ADVANCE trial in patients with relapsing-remitting multiple sclerosis (RRMS), peginterferon beta-1a [125 mcg subcutaneous

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(SC) injection every 2 weeks (Q2W)] significantly reduced the annualized relapse rate (ARR), 12- and 24-week confirmed disability worsening (CDW), and the number of new or newly enlarging T2 (NET2) lesions and new gadolinium-enhancing (Gd+) lesions over 1 year compared with placebo.^{5,6} Patients who received continuous treatment with peginterferon beta-1a Q2W over 2 years had sustained reductions in relapses and CDW, as well as significant reductions in NET2 lesions and new Gd+ lesions compared with patients who received placebo in year 1 (delayed treatment).⁷ In addition, the ADVANCE extension study, ATTAIN, demonstrated the sustained, long-term efficacy of peginterferon beta-1a Q2W over a period of up to 5 years.^{6,8}

GA SC 20 mg/ml has been evaluated in four randomized clinical studies in patients with RRMS, and has demonstrated significant benefit over placebo in the proportion of relapse-free patients and ARR over 2 years, the time to relapse over 3 years, and the cumulative number of Gd+ lesions over 9 months.⁴ In the GALA study, GA SC 40 mg/ml three times a week (TIW) was associated with significant improvement in ARR over 1 year compared with placebo.⁹ A head-to-head dose-comparison study of GA 20 mg/ml once daily (QD) and GA 40 mg/ml TIW demonstrated no differences in ARR outcomes between the two doses over 1 year.¹⁰ The sustained effectiveness of GA 20 mg/ml QD (for up to 6 years) and 40 mg/ml TIW (for up to 3 years) has been demonstrated in open-label extension (OLE) studies.^{11,12}

Comparative efficacy studies may offer important information for patients with multiple sclerosis and HCPs making decisions about disease-modifying therapies (DMTs). Head-to-head randomized interventional trials provide the strongest evidence of comparative efficacy; but in the absence of such trials, individual patient data from different studies can be compared using propensity score matching (PSM) methods to remove bias due to differences in significant covariates.^{13,14} When individual patient data are not readily available for inter-trial comparisons, matching-adjusted and indirect methods using aggregate data from treatment and placebo or control groups can provide helpful information.¹⁵⁻¹⁷

In order to evaluate the comparative efficacy of peginterferon beta-1a and GA, we performed two matching analyses of these two treatments. First,

we compared treatment efficacy at 2 years using individual patient data for peginterferon beta-1a 125 mcg Q2W and GA 20 mg/ml QD with a PSM analysis of the ADVANCE and CONFIRM studies. Second, we compared longer-term treatment efficacy of up to 3 years using individual patient data for peginterferon beta-1a 125 mcg Q2W and aggregate patient data for GA 40 mg/ml TIW with a matching-adjusted comparison (MAC) analysis of the ADVANCE, ATTAIN, and GALA studies.

Methods

Patients and studies

Patient-level data for peginterferon beta-1a were available from the ADVANCE and ATTAIN studies. ADVANCE [ClinicalTrials.gov identifier: NCT00906399] was a 2-year, randomized, double-blind phase III study of patients with RRMS randomized 1:1:1 to receive SC peginterferon beta-1a 125 mcg Q2W ($n=512$) or every 4 weeks (Q4W; $n=500$) or placebo ($n=500$) in year 1. Patients receiving placebo were re-randomized to receive SC peginterferon beta-1a 125 mcg Q2W or Q4W in year 2.^{5,7} ATTAIN [ClinicalTrials.gov identifier: NCT01332019] was an extension study of ADVANCE that evaluated the long-term safety, tolerability, and efficacy of peginterferon beta-1a 125 mcg Q2W and Q4W.⁶

Patient-level data on GA 20 mg/ml QD were available from CONFIRM [ClinicalTrials.gov identifier: NCT00451451], a 2-year, randomized, double-blind phase III study. Patients with RRMS were randomized 1:1:1:1 to oral placebo ($n=363$), oral dimethyl fumarate 240 mg twice daily ($n=359$) or three times daily ($n=345$), or SC GA 20 mg/ml QD ($n=350$).¹⁸

Aggregate data for patients treated with GA 40 mg/ml TIW were available from GALA [ClinicalTrials.gov identifier: NCT01067521], a 1-year, randomized phase III study. Patients with RRMS were randomized 2:1 to GA 40 mg/ml TIW ($n=943$) or placebo ($n=461$).⁹ In the 2-year GALA OLE study, patients who had received GA 40 mg/ml were maintained on active treatment and placebo patients were switched to GA 40 mg/ml TIW.¹²

Assessments

In both ADVANCE and CONFIRM, relapses were defined as new or recurrent neurologic

symptoms not associated with fever or infection, lasting ≥ 24 h, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses by ≥ 30 days.^{5,18} Definitions of relapses in GALA were similar to those in ADVANCE, with the exception that symptoms were required to last ≥ 48 h.

Expanded Disability Status Scale (EDSS) score was evaluated every 12 weeks and at the time of suspected relapse (evaluated during unscheduled visits) in ADVANCE, ATTAIN, CONFIRM, and GALA, and at 24-week intervals in the GALA OLE study. For these analyses, CDW was defined as an increase in EDSS score ≥ 1.0 point in patients with a baseline score ≥ 1.0 or an increase ≥ 1.5 points in patients with a baseline score of 0.0, confirmed after 12 or 24 weeks.

Clinical no evidence of disease activity (clinical-NEDA) was defined as no relapses or 12-week CDW; magnetic resonance imaging NEDA (MRI-NEDA) was defined as no NET2 or Gd+ lesions; and overall NEDA was defined as fulfillment of both clinical-NEDA and MRI-NEDA criteria.

Statistical analyses

Propensity score matching. PSM (1:1) based on key baseline covariates (age, baseline EDSS score, years from onset of symptoms, number of relapses in prior year, and sex) was performed on ADVANCE peginterferon beta-1a 125 mcg Q2W patients and CONFIRM GA 20 mg/ml QD patients.

Covariates that were imbalanced after PSM were included in the final outcome model using doubly robust estimation. ARR at 2 years in matched patients was estimated using a negative binomial regression with additional adjustment for baseline EDSS score, age (<40 *versus* ≥ 40 years), and number of relapses in the year prior to study entry. Cumulative probabilities of 12- and 24-week CDW at 2 years were evaluated using the Kaplan–Meier method. Hazard ratios (HRs), 95% confidence intervals (CIs), and *p* values were determined by Cox proportional-hazards modeling with additional adjustment for baseline EDSS score and age (<40 *versus* ≥ 40 years).

For NEDA analyses, data from peginterferon beta-1a patients in ADVANCE and GA patients in the MRI subcohort of CONFIRM¹⁹ were used to perform 2:1 PSM using baseline covariates

(age, baseline EDSS score, years from onset of symptoms, number of relapses in the prior year, sex, number of Gd+ lesions, and T2-weighted lesion volume). Patients assessed for NEDA were required to have ≥ 2 years of follow-up and to meet the specific NEDA criteria. Patients followed for <2 years, regardless of disease outcomes, were not counted as achieving NEDA. Missing data for NEDA assessments were treated using an observed-only approach. A separate analysis of MRI-NEDA and overall NEDA was carried out in patients with nonmissing clinical and MRI baseline characteristics.

For all PSM analyses, marginal significance at the type I error level of 0.05 was used.

Matching-adjusted comparison. To compare longer-term efficacy (over a period of up to 3 years), individual data from patients randomized to peginterferon beta-1a 125 mcg Q2W in year 1 of ADVANCE and continued peginterferon beta-1a in year 2 [the year 2 intent-to-treat (ITT) population] were matched to key baseline characteristics from available aggregate data of patients randomized to GA 40 mg/ml TIW in year 1 of GALA who entered the OLE (the year 2 OLE ITT population). The year 2 ITT populations thus included only those patients who received at least 1 year of active treatment, and did not include patients who had been treated with placebo in year 1. After matching, ARRs (calculated using negative binomial regression with adjustments for baseline EDSS score, log of the number of relapses in previous 2 years, status of Gd+ activity at baseline, volume of T2 lesions at baseline, and geographic region) in the year 2 peginterferon beta-1a ITT patient populations were calculated at 1 and 2 years (ADVANCE) and 3 years (ATTAIN) and compared with ARRs in GA patients in the corresponding years of GALA. As neither individual patient data nor proportions of patients with 12- or 24-week CDW at years 2 and 3 were available from GALA, a MAC analysis of CDW could not be performed. Data from patients randomized to placebo treatment in year 1 of ADVANCE or GALA were not included in this analysis.

For both matching comparisons, ARR was assessed as the primary analysis outcome. In the MAC analysis of ARR over 3 years, ARR at 1 year was the primary outcome and ARRs at years 2 and 3 were evaluated as secondary outcomes. Cumulative probabilities of 12- and 24-week CDW

Table 1. Baseline characteristics of patients treated with peginterferon beta-1a 125 mcg Q2W in ADVANCE and GA 20 mg/ml QD in CONFIRM before and after PSM.

Variable	Before PSM			After PSM		
	Peginterferon beta-1a (n=512)	GA (n=350)	Cohort p value	Peginterferon beta-1a (n=336)	GA (n=336)	Cohort p value
Age, mean (SD), year	36.9 (9.8)	36.7 (9.1)	0.681	37.1 (9.8)	36.6 (9.1)	0.573
Proportion female (SD)	0.7 (0.5)	0.7 (0.5)	0.984	0.7 (0.5)	0.7 (0.5)	1.000
EDSS score, mean (SD)	2.5 (1.3)	2.6 (1.2)	0.222	2.6 (1.2)	2.6 (1.2)	0.470
Time since symptom onset, mean (SD), year	6.9 (6.6)	7.1 (5.9)	0.604	7.3 (6.5)	7.1 (6.0)	0.781
Number of relapses in the prior year, mean (SD)	1.6 (0.7)	1.4 (0.6)	<0.001	1.4 (0.6)	1.4 (0.6)	0.899

EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; PSM, propensity score matching; Q2W, every 2 weeks; QD, once daily; SD, standard deviation.

NEDA (PSM) were also evaluated as secondary outcomes. As in the PSM analyses, marginal significance at the type I error level of 0.05 was used for the MAC analyses of ARR and CDW.

Data availability statement. The patient-level data sets generated and/or analyzed during the current study are not publicly available. The authors and company are fully supportive of allowing independent assessment and verification of these results. Requests for de-identified data, including the output files from the statistical analyses, should be made *via* the established company data-sharing policies and processes as detailed on the website <https://biogen-dt-external.pharmacm.com//DT/Home/Index/>. Additional details about data-sharing policies and procedures are provided in Supplemental File S1.

Results

PSM comparison of peginterferon beta-1a 125 mcg Q2W and GA 20 mg/ml QD

Patients. Before PSM, patients treated with peginterferon beta-1a 125 mcg Q2W ($n=512$) and GA 20 mg/ml QD ($n=350$) were well balanced for age, sex, EDSS score, and time since symptom onset; however, GA patients had significantly fewer relapses in the year prior to study enrollment ($p<0.001$). After matching, the peginterferon beta-1a and GA patients ($n=336$ each) were well matched in all categories (Table 1).

Clinical outcomes. In ADVANCE and CONFIRM, treatment with peginterferon beta-1a and GA significantly reduced ARR relative to placebo ($p<0.0001$ and $p=0.01$, respectively). A comparison of the propensity-score-matched patient populations indicated that at 2 years, ARR was significantly lower for patients treated with peginterferon beta-1a than for those treated with GA [0.204 *versus* 0.282; risk ratio (95% CI)=0.724 (0.527–0.993); $p=0.045$; Figure 1].

In the matched patient populations, patients who received continuous peginterferon beta-1a in ADVANCE also had a significantly lower cumulative probability of 12-week CDW at 2 years (96 weeks) than patients who received GA in CONFIRM [10.0% *versus* 14.6%; HR (95% CI)=0.625 (0.393–0.995); $p=0.048$; Figure 2(a)]. However, the cumulative probabilities of 24-week CDW with peginterferon beta-1a and GA at 2 years were not significantly different [7.7% *versus* 10.6%; HR (95% CI)=0.684 (0.398–1.178); $p=0.171$; Figure 2(b)].

NEDA. Matched groups for MRI-NEDA and overall NEDA analyses included 305 peginterferon beta-1a patients and 165 GA patients. Significantly higher percentages of peginterferon beta-1a patients than GA patients achieved MRI-NEDA [27.5% *versus* 16.4% ($p=0.014$)] and overall NEDA [20.3% *versus* 11.5% ($p=0.047$)] over 2 years (Figure 3). Clinical-NEDA rates over 2 years were compared using the entire PSM cohorts and were similar for the

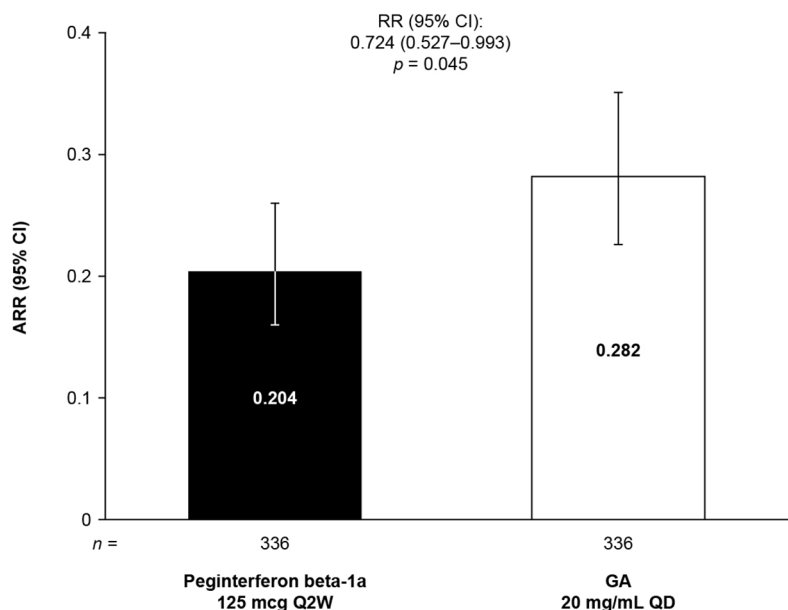


Figure 1. ARR at 2 years in propensity-score-matched patients treated with peginterferon beta-1a 125 mcg Q2W or GA 20 mg/ml QD. ARR were compared using negative binomial regression with adjustment for baseline EDSS score, age (<40 versus \geq 40 years), and the number of relapses in the year prior to study entry. ARR, annualized relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; Q2W, every 2 weeks; QD, once daily; RR, risk ratio.

matched peginterferon beta-1a and GA ($n = 336$ each) patients (56.0% versus 55.1%; $p = 0.762$; Figure 3).

NEDA results were similar in the subpopulation of patients with nonmissing baseline characteristics for whom MRI-NEDA or overall NEDA could be determined. MRI-NEDA was achieved by 83 of 257 patients (32.3%) on peginterferon beta-1a and 26 of 136 patients (19.1%) on GA ($p = 0.009$). Overall NEDA was achieved by 67 of 274 patients (24.5%) on peginterferon beta-1a and 19 of 147 patients (12.9%) on GA ($p = 0.009$).

Matching-adjusted comparison of peginterferon beta-1a 125 mcg Q2W and GA 40 mg/ml TIW. Key baseline characteristics in the peginterferon beta-1a (ADVANCE, $n = 407$) and GA (GALA, $n = 834$) year 2 ITT patient populations are shown in Table 2. After matching, key baseline characteristics in the peginterferon beta-1a (effective $n = 276$) and GA ($n = 834$) year 2 ITT populations were identical. In a comparative analysis of the matched populations, ARR did not differ significantly in patients treated with peginterferon beta-1a Q2W from those treated with GA 40 mg/ml TIW at 1 year (0.278 versus 0.318; $p = 0.375$), whereas

ARR was significantly lower in the former group than the latter at both 2 years (0.090 versus 0.203; $p = 0.032$) and 3 years (0.109 versus 0.209; $p = 0.047$; Figure 4).

Discussion

The two comparative analyses described here indicate that patients with RRMS treated with peginterferon beta-1a 125 mcg Q2W generally achieved better clinical outcomes than patients treated with GA 20 mg/ml QD or GA 40 mg/ml TIW. However, some of the differences observed here are relatively modest. Care should therefore be exercised when drawing conclusions of clinical significance, especially on the basis of analyses with wide CIs.

Significantly lower ARR were observed after 2 years in patients treated with peginterferon beta-1a Q2W than in those treated with GA 20 mg/ml QD (PSM analysis). The PSM analysis also demonstrated a reduction in the cumulative probability of 24-week CDW at 2 years in patients treated with peginterferon beta-1a Q2W compared with those treated with GA 20 mg/ml QD. It should be noted that, while

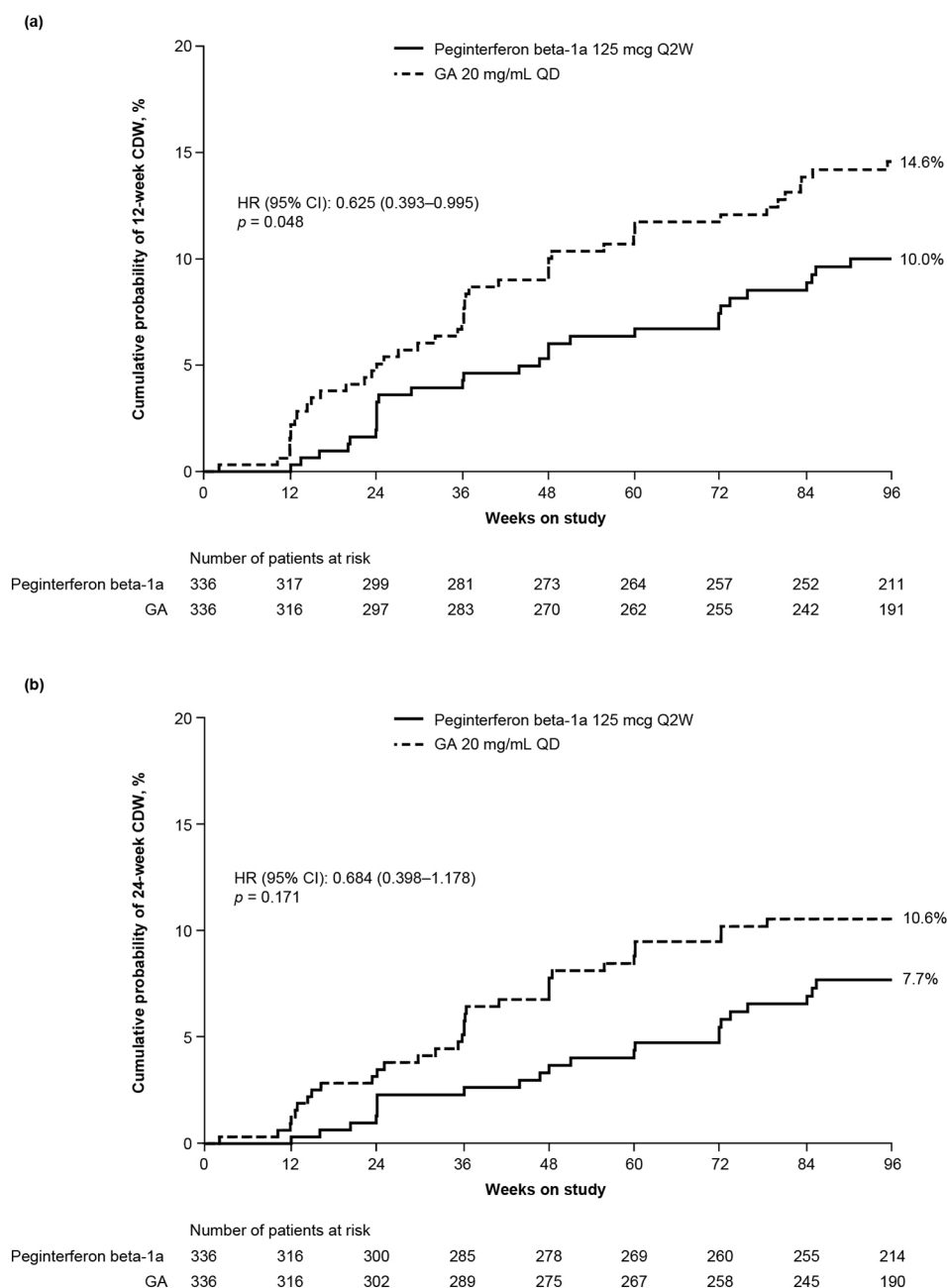


Figure 2. (a) 12-week and (b) 24-week CDW over 2 years in propensity-score-matched patients treated with peginterferon beta-1a 125 mcg Q2W or GA 20 mg/ml QD. HR, 95% CI, and *p* value are from Cox proportional-hazards regression with adjustment for baseline EDSS score and age (<40 versus ≥40 years). CDW, confirmed disability worsening; CI, confidence interval; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; HR, hazard ratio; Q2W, every 2 weeks; QD, once daily.

CONFIRM was not specifically designed to test superiority or noninferiority of GA,¹⁸ the number of patients randomized to GA 20 mg/ml QD in that study is sufficient for the PSM

comparison described here. In addition, significantly lower ARRs were observed in the MAC analysis of patients treated with peginterferon beta-1a Q2W compared with those treated with

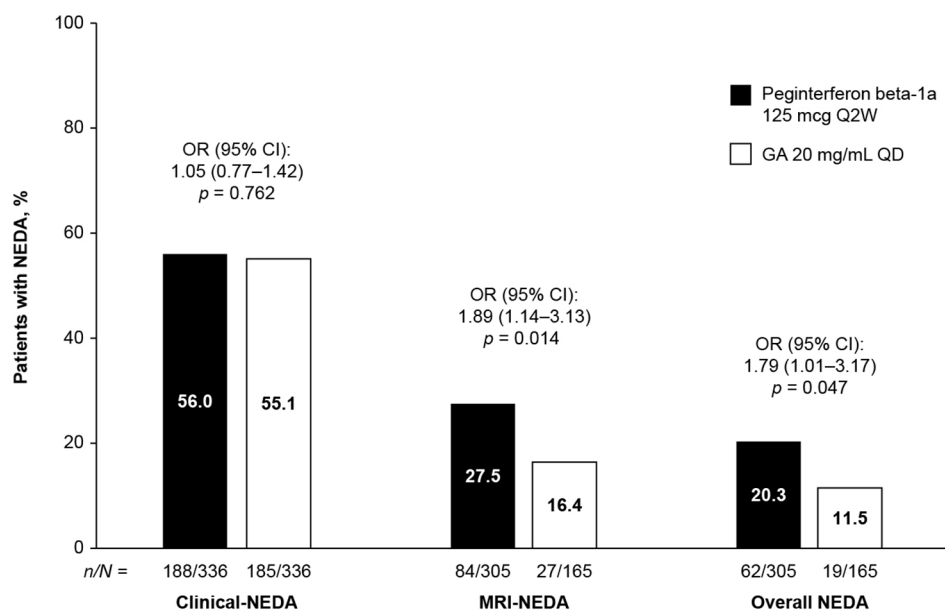


Figure 3. Clinical-NEDA, MRI-NEDA, and overall NEDA over 2 years in propensity-score-matched patients treated with peginterferon beta-1a 125 mcg Q2W or GA 20 mg/ml QD. Missing data were treated using an observed-only approach. For clinical-NEDA, *p* value is based on logistic regression adjusted for baseline EDSS score, years from onset of symptoms, and sex. For MRI-NEDA and overall NEDA, *p* values are based on logistic regression adjusted for baseline EDSS score, years from symptoms onset, sex, number of Gd+ lesions, and volume of T2 lesions.

CI, confidence interval; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity; OR, odds ratio of peginterferon beta-1a *versus* GA; Q2W, every 2 weeks; QD, once daily.

Table 2. Baseline characteristics of year 2 ITT patients treated with peginterferon beta-1a 125 mcg Q2W in ADVANCE/ATTAIN or with GA 40 mg/mL TIW in GALA before and after matching.

Characteristic	Peginterferon beta-1a before matching (n=407)	Peginterferon beta-1a after matching (n=276) ^a	GA (n=834)
Age, mean (SD)	36.4 (9.4)	37.3 (9.3)	37.3 (9.3)
Female, n (%)	288 (70.8)	185 (67.0)	559 (67.0)
Years since symptom onset, mean (SD)	6.5 (6.4)	7.7 (6.8)	7.7 (6.8)
Baseline EDSS score	2.4 (1.3)	2.8 (1.2)	2.8 (1.2)
Number of Gd+ lesions at baseline, mean (SD)	1.2 (3.5)	1.7 (4.9)	1.7 (4.9)

ITT patient populations consisted of patients randomized to receive peginterferon beta-1a 125 mcg Q2W or GA 40 mg/mL TIW in study year 1 and who entered year 2 after completion of year 1.

^aEffective *n*.

EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; Gd+, gadolinium enhancing; ITT, intent to treat; Q2W, every 2 weeks; SD, standard deviation; TIW, three times a week.

GA 40 mg/ml TIW at 2 and 3 years. There was, however, no difference in ARR at 1 year of treatment between the two DMTs. Taken together,

these results suggest that differences in ARR between peginterferon beta-1a and GA are observed after 2 years of treatment.

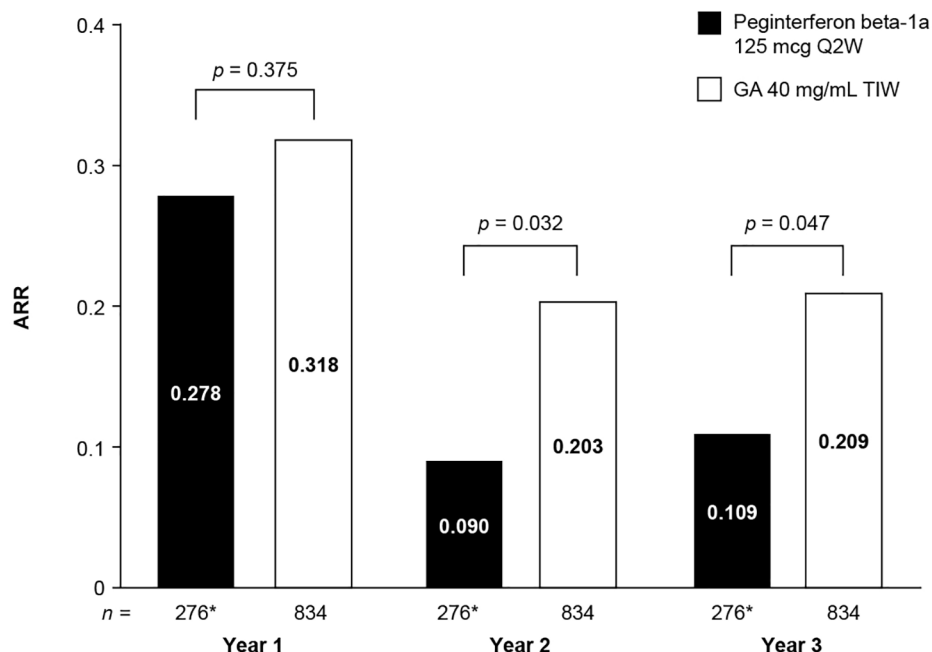


Figure 4. MAC analysis of ARR in the matched year 2 ITT patient populations treated with peginterferon beta-1a 125 mcg Q2W (ADVANCE/ATTAIN) or GA 40 mg/ml TIW (GALA) in study years 1–3. Analysis includes patients randomized to peginterferon beta-1a 125 mcg Q2W or GA 40 mg/ml TIW in year 1 of ADVANCE or GALA, respectively, who completed study year 1 and started year 2.

*Effective *n*.

ARR, annualized relapse rate; GA, glatiramer acetate; ITT, intent-to-treat; MAC, matching-adjusted comparison; Q2W, every 2 weeks; TIW, three times a week.

In the PSM analysis of peginterferon beta-1a Q2W and GA 20 mg/ml QD, a significantly higher proportion of peginterferon beta-1a patients than GA patients achieved MRI-NEDA and overall NEDA over 2 years of treatment. Achieving NEDA has been proposed as a principal aim for neurologists in their practices.²⁰ It should be noted that the prognostic significance of NEDA has yet to be firmly established, and that, while some studies have found an association between achieving NEDA in the first 2 years of treatment and favorable longer-term outcomes,²¹ others have failed to do so.²²

Treatment outcomes for peginterferon beta-1a and GA have been assessed in prior mixed-treatment comparison analyses and meta-analyses of randomized clinical trial data. A meta-analysis of 13 clinical trials showed a lower risk ratio for disability progression in RRMS patients treated with peginterferon beta-1a Q2W *versus* placebo in ADVANCE (0.61; 95% CI, 0.43–0.88) than with either GA 20 mg/ml QD *versus* placebo in CONFIRM (0.77; 95% CI, 0.54–1.09) or 40 mg/ml TIW *versus* placebo in GALA (1.21; 95% CI, 0.70–2.10).²³

In addition, a network meta-analysis of 28 clinical trials demonstrated that treatment with peginterferon beta-1a 125 mcg Q2W resulted in reductions in 12- and 24-week CDW of 38% and 45%, respectively, *versus* placebo, whereas treatment with GA 20 mg/ml QD resulted in reductions of 19% and 25%, respectively, *versus* placebo.²⁴ The network analysis did not identify any difference in comparative ARR (defined as the mean number of confirmed protocol-defined relapses per patient, adjusted for the duration of follow-up) between peginterferon beta-1a and either GA dosing regimen. These observations are consistent with those from another network meta-analysis comparing the relative efficacy of peginterferon beta-1a *versus* other injectable first-line DMTs, including GA, which showed a numerical trend favoring peginterferon beta-1a 125 mcg Q2W *versus* GA 20 mg/ml QD for 12- and 24-week CDW but not for ARR.²⁵ Two recent network meta-analyses also demonstrated no difference in efficacy between peginterferon beta-1a and either regimen of GA on ARR,^{26,27} though a positive impact on risk of disease

progression was shown for peginterferon beta-1a 125 mcg Q2W compared with GA 20 mg/ml QD.²⁶

Comparative effectiveness research is an important tool in the evaluation of different therapies by HCPs and regulatory authorities.²⁸ In the absence of randomized head-to-head trials, comparative evidence can be obtained using statistical approaches to match individual and aggregate patient data from different clinical trials or observational studies.¹⁴ However, indirect comparisons, including PSM and MAC, have important limitations. All indirect comparisons have a potential for bias due to the presence of unobserved, thus nonbalanced, confounders in the treatment populations. These methods, while helping balance measured covariates between two different treatment groups, rely on the identification and selection of appropriate covariates for analysis. It is unlikely that covariate selection for matching will take into account all relevant confounders. Further, unobserved covariates that affect treatment allocation or treatment outcome are not accounted for in the matching procedure.²⁹ Differences in study protocols, including inclusion and exclusion criteria, might also have affected our results. Indeed, MRI-NEDA and overall NEDA analyses were not performed in the MAC analysis of patients from ADVANCE/ATTAIN and GALA due to the lack of standardized MRI acquisition protocols across studies. In addition, for matching-adjusted methods that rely on aggregate data, the reduction in sample size after matching reduces the statistical power of the analysis, and the generalizability of the findings is limited to patients with baseline characteristics similar to those in the matching analysis. The limited availability of published aggregate baseline covariate data can also impact the ability to conduct comparative analyses on common clinical outcomes. Finally, the MAC analysis used here is limited by the lack of a common comparator arm^{30,31} between the ADVANCE and GALA studies beyond 1 year.

The safety and tolerability of peginterferon beta-1a and GA could not be compared in this study due to variability in safety reporting across the studies. A recent network meta-analysis of safety outcomes of available DMTs for RRMS identified a higher risk of discontinuation due to adverse events with peginterferon beta-1a 125 mcg Q2W than with GA 20 mg/ml QD,³² though the study also noted considerable variability in safety out-

come reporting, which made comparisons of different trials difficult.

The results of the matching analyses presented here suggest that SC peginterferon beta-1a 125 mcg Q2W may provide better ARR, 12-week CDW, and MRI- and overall NEDA outcomes than SC GA 20 mg/ml QD at 2 years and better ARR outcomes at 2 and 3 years than GA 40 mg/ml TIW. In the absence of head-to-head randomized comparisons of these two therapies, the results described here can provide information for HCPs and patients deciding on first-line treatments for RRMS.

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Conflict of interest statement

TFS has received research support from Biogen, Genentech, and Novartis and speaker fees and honoraria for participation in scientific advisory boards from Acorda, Biogen, Genentech, Genzyme, Novartis, and Teva Neuroscience.

RS and KX are former employees of and may own stock and/or stock options in Biogen.

AA, CC-V, and MLN are employees of and may own stock and/or stock options in Biogen.

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Supplemental material

Supplemental material for this article is available online.

References

1. Montalban X, Gold R, Thompson AJ, *et al.*ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Eur J Neurol* 2018; 25: 215–237.
2. Rae-Grant A, Day GS, Marrie RA, *et al.* Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the guideline development, dissemination, and implementation subcommittee of the American academy of neurology. *Neurology* 2018; 90: 777–788.
3. Plegridy [prescribing information]. Cambridge, MA: Biogen Inc., 2019.
4. Copaxone [prescribing information] Kansas City, MO: Teva Neuroscience, 2019.
5. Calabresi PA, Kieseier BC, Arnold DL, *et al.* Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *Lancet Neurol* 2014; 13: 657–665.
6. Newsome SD, Scott TF, Arnold DL, *et al.* Long-term outcomes of peginterferon beta-1a in multiple sclerosis: results from the ADVANCE extension study, ATTAIN. *Ther Adv Neurol Disord* 2018; 11: 1756286418791143.
7. Kieseier BC, Arnold DL, Balcer LJ, *et al.* Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE. *Mult Scler* 2015; 21: 1025–1035.
8. Arnold DL, Shang S, Dong Q, *et al.* Peginterferon beta-1a every 2 weeks increased achievement of no evidence of disease activity over 4 years in the ADVANCE and ATTAIN studies in patients with relapsing-remitting multiple sclerosis. *Ther Adv Neurol Disord* 2018; 11: 1756286418795085.
9. Khan O, Rieckmann P, Boyko A, *et al.*; GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Ann Neurol* 2013; 73: 705–713.
10. Comi G, Cohen JA, Arnold DL, *et al.*; FORTE Study Group. Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. *Ann Neurol* 2011; 69: 75–82.
11. Johnson KP, Brooks BR, Ford CC, *et al.* Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. *Mult Scler* 2000; 6: 255–266.
12. Khan O, Rieckmann P, Boyko A, *et al.* Efficacy and safety of a three-times-weekly dosing regimen of glatiramer acetate in relapsing-remitting multiple sclerosis patients: 3-year results of the glatiramer acetate low-frequency administration open-label extension study. *Mult Scler* 2017; 23: 818–829.
13. Rosenbaum PR and Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc* 1984; 79: 516–524.
14. Trojano M, Tintore M, Montalban X, *et al.* Treatment decisions in multiple sclerosis—insights from real-world observational studies. *Nat Rev Neurol* 2017; 13: 105–118.
15. Bucher HC, Guyatt GH, Griffith LE, *et al.* The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997; 50: 683–691.
16. Riley RD, Simmonds MC and Look MP. Evidence synthesis combining individual patient data and aggregate data: a systematic review identified current practice and possible methods. *J Clin Epidemiol* 2007; 60: 431–439.
17. Coyle PK, Shang S, Xiao Z, *et al.* Matching-adjusted comparisons demonstrate better clinical outcomes with SC peginterferon beta-1a every two weeks than with SC interferon beta-1a three times per week. *Mult Scler Relat Disord* 2018; 22: 134–138.
18. Fox RJ, Miller DH, Phillips JT, *et al.* Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012; 367: 1087–1097.
19. Miller DH, Fox RJ, Phillips JT, *et al.* Effects of delayed-release dimethyl fumarate on MRI measures in the phase 3 CONFIRM study. *Neurology* 2015; 84: 1145–1152.
20. Giovannoni G, Tomic D, Bright JR, *et al.* No evident disease activity: the use of combined assessments in the management of patients with multiple sclerosis. *Mult Scler* 2017; 23: 1179–1187.
21. Goodin DS, Reder AT, Traboulsee AL, *et al.* Predictive validity of NEDA in the 16- and 21-year follow-up from the pivotal trial of interferon beta-1b. *Mult Scler* 2019; 25: 837–847.

22. University of California San Francisco-MS Epic Team, Cree BAC, Hollenbach JA, *et al.* Silent progression in disease activity-free relapsing multiple sclerosis. *Ann Neurol* 2019; 85: 653–666.
23. Tsivgoulis G, Katsanos AH, Grigoriadis N, *et al.* The effect of disease modifying therapies on disease progression in patients with relapsing-remitting multiple sclerosis: a systematic review and meta-analysis. *PLoS One* 2015; 10: e0144538.
24. Fogarty E, Schmitz S, Tubridy N, *et al.* Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: systematic review and network meta-analysis. *Mult Scler Relat Disord* 2016; 9: 23–30.
25. Tolley K, Hutchinson M, You X, *et al.* A network meta-analysis of efficacy and evaluation of safety of subcutaneous pegylated interferon beta-1a versus other injectable therapies for the treatment of relapsing-remitting multiple sclerosis. *PLoS One* 2015; 10: e0127960.
26. Hamidi V, Couto E, Ringerike T, *et al.* A multiple treatment comparison of eleven disease-modifying drugs used for multiple sclerosis. *J Clin Med Res* 2018; 10: 88–105.
27. Lucchetta RC, Tonin FS, Borba HH, *et al.* Disease-modifying therapies for relapsing-remitting multiple sclerosis: a network meta-analysis. *CNS Drugs* 2018; 32: 813–826.
28. Sox HC and Greenfield S. Comparative effectiveness research: a report from the institute of medicine. *Ann Intern Med* 2009; 151: 203–205.
29. Garrido MM, Kelley AS, Paris J, *et al.* Methods for constructing and assessing propensity scores. *Health Serv Res* 2014; 49: 1701–1720.
30. Phillippo DM, Ades AE, Dias S, *et al.* Methods for population-adjusted indirect comparisons in health technology appraisal. *Med Decis Making* 2018; 38: 200–211.
31. Signorovitch JE, Sikirica V, Erder MH, *et al.* Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health* 2012; 15: 940–947.
32. Lucchetta RC, Leonart LP, Becker J, *et al.* Safety outcomes of disease-modifying therapies for relapsing-remitting multiple sclerosis: a network meta-analysis. *Mult Scler Relat Disord* 2019; 35: 7–15.

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