



Comparative efficacy of diroximel fumarate, ozanimod and interferon beta-1a for relapsing multiple sclerosis using matching-adjusted indirect comparisons

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Aim: Diroximel fumarate (DRF), ozanimod (OZA) and interferon beta-1a (IFN) are disease-modifying therapies approved for the treatment of relapsing multiple sclerosis. No randomized trials have compared DRF versus OZA and IFN. We compared DRF versus OZA and DRF versus IFN using matching-adjusted indirect comparisons for efficacy outcomes, including annualized relapse rate (ARR), 12- and 24-week confirmed disability progression (CDP) and absence of gadolinium-enhancing (Gd+) T1 lesions and new/newly enlarging T2 lesions. **Patients & methods:** We used individual patient data from EVOLVE-MS-1 (NCT02634307), a 2-year, open-label, single-arm, phase III study of DRF (n = 1057) and aggregate data from RADIANCE (NCT02047734), a 2-year, double-blind, phase III study that compared OZA 1 mg once daily (n = 433) and intramuscular IFN 30 µg once weekly (n = 441). To account for cross-trial differences, the EVOLVE-MS-1 population was restricted to those who met the inclusion/exclusion criteria for RADIANCE, then weighted to match the average baseline characteristics of RADIANCE. **Results:** After weighting, DRF and OZA had similar ARRs (0.18 and 0.17, respectively), with a rate difference (DRF vs OZA) of 0.01 (95% confidence interval [CI]: -0.04 to 0.06). DRF had a lower ARR than IFN (0.18 and 0.28, respectively), with a rate difference (DRF vs IFN) of -0.10 (95% CI: -0.16 to -0.04) after weighting. Outcomes for 12- and 24-week CDP favored DRF versus OZA; 12-week CDP favored DRF versus IFN, but there was not strong evidence favoring DRF over IFN for 24-week CDP. Compared with OZA and IFN, DRF had higher proportions of patients without Gd+ T1 lesions and patients without new/newly enlarging T2 lesions. **Conclusion:** Disability progression and radiological outcomes were favorable for DRF versus OZA, although no differences were observed in ARR. Clinical and radiological outcomes generally favored DRF versus IFN. These findings may be informative for patients and clinicians considering different treatment options for MS.

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Multiple sclerosis (MS) is a chronic, debilitating disease of the central nervous system (CNS) that affects over 900,000 people in the US and 2.9 million people globally [1–3]. Activated immune cells invade the CNS, which causes inflammation, demyelination, axonal loss and gliosis in patients with MS [4,5]. Most patients with MS (85%) have relapsing-remitting MS (RRMS), a form of MS that is characterized by episodes of relapses followed

by a period of remission [3]. In the absence of treatment, patients with RRMS may experience frequent relapses with increasing disability, develop more progressive forms of MS (e.g., secondary progressive MS) and have poorer quality of life [6,7].

Several classes of disease-modifying therapies (DMTs) with different modes of action have emerged as effective options for managing MS symptoms and reducing disease progression, including fumarates, interferons and sphingosine 1-phosphate receptor modulators (S1PRMs) [8–13]. Evidence of the comparative efficacy of DMTs may be useful for clinicians and patients in making informed treatment decisions, as well as for reimbursement and regulatory agencies.

Diroximel fumarate (DRF), an oral DMT taken twice daily, was approved based on its bioequivalence with dimethyl fumarate (DMF) and has demonstrated better gastrointestinal (GI) tolerability and fewer discontinuations compared with DMF [14]. DRF is believed to exert its therapeutic effects by reducing inflammation and oxidative stress via activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway by its active metabolite, monomethyl fumarate (MMF) [8]. Ozanimod (OZA), an oral S1PRM approved for the treatment of relapsing forms of MS, acts by retaining lymphocytes in lymphoid tissues, thereby reducing their migration into the CNS and limiting immune-mediated damage [15]. Interferon beta-1a (IFN) is an injectable DMT used in the treatment of MS and exerts its effects by modulating the immune response and reducing inflammation in the CNS [16,17].

Although there are several studies comparing DMF with S1PRMs and IFN [18–21], comparative efficacy data of DRF with other DMTs are limited [22]. Comparisons of the efficacy of DRF versus OZA and of DRF versus IFN would be of value to patients and clinicians in selecting treatment options, but no randomized trials have directly compared DRF versus OZA or IFN. Rather, these DMTs have been examined in separate trials (DRF in the phase III EVOLVE-MS-1 trial; OZA and IFN in the phase III RADIANCE trial) [23–25]. Briefly, results from RADIANCE indicated favorable adjusted annualized relapse rate (ARR) and radiological outcomes for OZA 1.0 mg versus IFN and similar proportions of 12- and 24-week confirmed disability progression (CDP) between the two DMTs [24].

Due to differences in trial designs and baseline patient characteristics, crude comparisons of the reported outcomes of DRF-treated patients in EVOLVE-MS-1 with OZA- or IFN-treated patients in RADIANCE are likely to be biased. To improve the comparability of the trial populations, we used an indirect treatment comparison method known as matching-adjusted indirect comparison (MAIC). MAICs can be used to adjust for cross-trial differences and compare the efficacy of DMTs evaluated in separate studies [26]. The objective of this study was to compare the efficacy of DRF versus OZA and DRF versus IFN for ARR, 12-week CDP, 24-week CDP, absence of gadolinium-enhancing (Gd+) T1 lesions and absence of new/newly enlarging T2 lesions using MAICs.

Patients & methods

Study sample

EVOLVE-MS-1 (ClinicalTrials.gov identifier: NCT02634307) was a 2-year, open-label, single-arm, phase III study in which all patients received DRF 462 mg twice daily ($n = 1057$; [Figure 1](#)) [23,25]. The EVOLVE-MS-1 study population included newly enrolled patients and patients who rolled over from the 5-week, randomized, double-blind, phase III EVOLVE-MS-2 study (ClinicalTrials.gov identifier: NCT03093324), which examined the GI tolerability of DRF and DMF [14]. We had individual patient data (IPD) from EVOLVE-MS-1.

RADIANCE (ClinicalTrials.gov identifier: NCT02047734) was a 2-year, double-blind, phase III study in which patients were randomized to and received at least one dose of OZA 1 mg once daily ($n = 433$), OZA 0.5 mg once daily ($n = 439$), or IFN beta-1a 30 µg once weekly ($n = 441$). The study designs are summarized in [Figure 1](#). Aggregate data from RADIANCE were obtained from published results [24]. The OZA 0.5-mg arm was not examined in the current analysis since it does not correspond with the approved OZA full dosage. In order to match the trial populations, EVOLVE-MS-1 data were restricted based on the inclusion and exclusion criteria used in the RADIANCE trial, and IPD were weighted so that their weighted baseline characteristics matched the average baseline characteristics in RADIANCE. Consistent with the inclusion and exclusion criteria of RADIANCE, we restricted the EVOLVE-MS-1 sample to patients who were aged between 18–55 (inclusive) years at baseline, had an Expanded Disability Status Scale (EDSS) score between 0 and 5.0 at baseline and had one or more relapses within the last 12 months prior to screening ([Supplementary Table 1](#)) [24]. Exclusion criteria that were applied to the EVOLVE-MS-1 sample were: patients with a disease duration of >15 years and EDSS ≤ 2.0 , a lymphocyte count $<0.8 \times 10^3/\mu\text{l}$ and >20 Gd+ lesions on a baseline brain MRI scan.



Figure 1. Study designs of EVOLVE-MS-1 and RADIANCE [23,24]. The OZA 0.5-mg arm of RADIANCE was not examined in the current analysis since it does not correspond with the approved OZA full dosage.

^aAdapted from Naismith et al. [23] licensed under CC-BY-NC 4.0 (<http://creativecommons.org/licenses/by-nc/4.0/>).

^bA subset of patients (n = 464; 43.9%) in EVOLVE-MS-1 rolled over from the 5-week, phase III EVOLVE-MS-2 study (NCT03093324) of DRF or dimethyl fumarate. Efficacy outcomes were assessed only in EVOLVE-MS-1.

^cA 2-week safety follow-up was required for all patients in EVOLVE-MS-1; lymphocyte monitoring follow-up visits were required for a further 6 months for patients who discontinued or completed treatment with absolute lymphocyte count $<0.8 \times 10^9/\text{l}$.

^dIn the event of a suspected relapse, unscheduled relapse visits were conducted.

D: Day; DRF: Diroximel fumarate; E: 7-day dose escalation; EDSS: Expanded Disability Status Scale; IFN: Interferon beta-1a; OZA: Ozanimod.

Definition & assessment of outcomes

Clinical outcomes were ARR and CDP sustained for 12 and 24 weeks, while radiological end points were absence of Gd+ T1 lesions and absence of new/newly enlarging T2 lesions. In RADIANCE the definition of CDP was progression of disability that was sustained for 12 weeks or 24 weeks defined by ≥ 1.0 point from baseline EDSS [24]; this definition of CDP was applied to EVOLVE-MS-1 to increase the comparability of the definition of 12- and 24-week CDP across studies. Absence of new/newly enlarging T2 lesions were assessed using MRI. In EVOLVE-MS-1, brain MRIs were obtained at baseline and weeks 48 and 96 [27]. In RADIANCE, brain MRIs were obtained at baseline and weeks 52 and 104 [24]. The proportion of patients with these MRI end points at week 96 in EVOLVE-MS-1 were compared with the proportion of patients with these MRI end points at week 104 in RADIANCE.

Statistical analysis

Baseline characteristics were compared in the original EVOLVE-MS-1 population (n = 1057), the EVOLVE-MS-1 sample after applying restrictions based on the inclusion and exclusion criteria for RADIANCE (n = 460) (Supplementary Table 1), the OZA 1 mg arm (n = 433) in RADIANCE and the IFN 30 μg (n = 441) in RADIANCE. Binary variables were summarized using proportions and continuous variables using means and standard deviations.

To account for cross-trial differences in observed baseline characteristics, unanchored MAIC analyses were conducted. An unanchored analysis was performed due to the lack of a common comparator between EVOLVE-

MS-1 and RADIANCE. Individuals in the restricted EVOLVE-MS-1 sample ($n = 460$) were assigned weights that corresponded to their odds of being enrolled in RADIANCE versus EVOLVE-MS-1. Weights were estimated using the method of moments to balance the mean covariate values between the weighted EVOLVE-MS-1 population and RADIANCE, such that after weighting, the baseline means of continuous variables and the baseline proportions for binary variables matched those reported in the OZA and IFN arms of RADIANCE [24]. Baseline variables used to estimate weights were those that may be both prognostic factors and effect modifiers: age, sex, race, number of relapses in the 12 months prior to study entry, EDSS score, Gd+ lesions, MS DMT history, time since first MS symptom and study site in Eastern Europe [28–30]. DRF-treated patients from EVOLVE-MS-1 were weighted separately to match the baseline characteristics of either the OZA or IFN arm of RADIANCE, respectively.

After weighting patients in EVOLVE-MS-1, the efficacy of DRF versus OZA and DRF versus IFN for ARR, 12-week and 24-week CDP, absence of Gd+ T1 lesions and absence of new/newly enlarging T2 lesions was compared. ARR was estimated in the weighted EVOLVE-MS-1 population using Poisson regression and included the natural log transformation of time on study as an offset term, consistent with the approach used in RADIANCE to analyze ARR [24]. The rate differences and rate ratios comparing the weighted ARR in DRF-treated patients with the observed ARRs in OZA- and IFN-treated patients were calculated. The risks of 12- and 24-week CDP in the weighted EVOLVE-MS-1 sample were estimated using the Kaplan–Meier product-limit method and then risk differences and risk ratios were calculated for DRF versus OZA and DRF versus IFN for 12- and 24-week CDP. The proportions of patients without Gd+ T1 lesions and new/newly enlarging T2 lesions were calculated using non-responder imputation, consistent with the approach taken in RADIANCE to analyze these MRI outcomes [24]. Non-responder imputation involves imputing patients missing MRI data as not being lesion-free. Risk differences and risk ratios for MRI outcomes were calculated for DRF versus OZA and DRF versus IFN. Bootstrapping with 1000 samples of the entire MAIC weighting process was used to obtain confidence intervals (CIs) around the weighted estimates to account for uncertainty in the sampling error and uncertainty in the weights.

We conducted two sensitivity analyses. The first sensitivity analysis aimed to address differences in length of follow-up between RADIANCE (104 weeks) and EVOLVE-MS-1 (96 weeks) by estimating radiological outcomes for EVOLVE-MS-1 at 104 weeks of follow-up. To estimate the risk of these MRI outcomes if there had been 104 weeks of follow-up in EVOLVE-MS-1, we used the following formula to convert an incidence rate to a risk: $\text{Risk} \approx \text{Incidence rate} \times \text{Time}$. We multiplied the observed rates of having a Gd+ T1 lesion or a new/newly enlarging T2 lesion in EVOLVE-MS-1 (with person-weeks in the denominator) by 104 weeks. This approach assumes that the incidence rate is constant over the time period, with no competing risks, and that the risk is low [31]. We then subtracted the risk of each outcome from 1 to obtain the proportion of patients free of Gd+ T1 lesions and new/newly enlarging T2 lesions.

The second sensitivity analysis sought to examine the impact of including patients who rolled over from EVOLVE-MS-2 in this analysis. Patients from EVOLVE-MS-2 who rolled over into EVOLVE-MS-1 were re-baselined at the start of EVOLVE-MS-1, which may impact radiological outcomes since residual disease activity may occur during the early phase of treatment for newly enrolled patients. The second sensitivity analysis aimed to address this by excluding the rollover population.

Results

Characteristics of study patients

After restrictions based on age, EDSS score, disease activity, disease duration, lymphocyte count and number of Gd+ lesions at baseline, 460 patients were retained from the EVOLVE-MS-1 population for this analysis. Patient baseline characteristics of both studies are presented in Table 1; after restricting and weighting, baseline characteristics between DRF versus OZA and DRF versus IFN treatment groups were balanced.

DRF versus OZA

The ARR, CDP and radiological outcomes after restriction and weighting are summarized in Table 2. ARR outcomes were similar for DRF and OZA; the ARR for DRF-treated patients was 0.18 (95% CI: 0.14–0.22), compared with 0.17 (95% CI: 0.14–0.21) in OZA-treated patients, corresponding with a rate difference of 0.01 (95% CI: -0.04 to 0.06) (Figure 2). Outcomes for 12- and 24-week CDP favored DRF versus OZA (Table 2; Figure 3); risk differences were -6.4% (95% CI: -10.3% to -2.4%) for 12-week CDP and -5.1% (95% CI: -8.9% to -1.6%) for 24-week CDP. DRF-treated patients were more likely to be free of Gd+ T1 lesions; 77.6% (95% CI: 73.0%–82.3%) did not have Gd+ T1 lesions compared with 65.6% (95% CI: 61.1%–70.1%) of OZA-treated

Table 1. Baseline characteristics before and after restriction and matching-adjusted indirect comparison weighting.

	EVOLVE-MS-1		DRF vs OZA		DRF vs IFN β -1a	
	DRF original sample (n = 1057)	DRF restricted sample (n = 460) [†]	EVOLVE-MS-1, DRF after weighting to match baseline characteristics of OZA (ESS = 298)	RADIANCE, OZA 1 mg arm (n = 433) [‡]	EVOLVE-MS-1, DRF after weighting to match baseline characteristics of IFN (ESS = 298)	RADIANCE, IFN β -1a 30 μ g arm (n = 441) [‡]
Age, years, mean (SD)	42.5 (10.8)	38.1 (9.1)	36.0 (9.0)	36.0 (8.9)	35.1 (9.0)	35.1 (9.1)
Female (%)	72.1	70.7	67.2	67.2	68.9	68.9
White (%)	92.0	92.6	98.8	98.8	98.0	98.0
Relapses in 12 months before study entry, n, mean (SD)	0.72 (0.77)	1.3 (0.55)	1.3 (0.54)	1.3 (0.56)	1.3 (0.54)	1.3 (0.58)
EDSS score, mean (SD)	2.7 (1.5)	2.4 (1.2)	2.6 (1.1)	2.6 (1.2)	2.5 (1.1)	2.5 (1.2)
Gd+ lesions (%)	29.6	37.8	41.1	41.1	44.4	44.4
DMT history (%)	64.4	47.2	28.4	28.4	28.6	28.6
Time since first MS symptom, years, mean (SD)	9.8 (8.3)	6.3 (6.2)	6.9 (6.4)	6.9 (6.2)	6.4 (6.0)	6.4 (6.1)
Eastern Europe (%)	53.2	55.9	86.4	86.4	85.9	85.9

[†] EVOLVE-MS-1 sample was restricted to those who met the inclusion and exclusion criteria used in RADIANCE based on age, EDSS, disease activity, disease duration, lymphocyte count and Gd+ lesions.

[‡] Data on baseline characteristics in RADIANCE's ozanimod and interferon beta-1a arms were obtained from Cohen *et al.* [24].

DMT: Disease-modifying therapy; DRF: Diroximel fumarate; EDSS: Expanded Disability Status Scale; ESS: Effective sample size; Gd+: Gadolinium-enhancing; IFN β -1a: Interferon beta-1 α ; MS: Multiple sclerosis; OZA: Ozanimod; SD: Standard deviation.

patients. Similarly, a higher proportion of DRF-treated patients (33.6% [95% CI: 28.8%–38.7%]) had an absence of new/newly enlarging T2 lesions than OZA-treated patients (23.8% [95% CI: 19.8%–27.8%]; [Figure 4](#)).

DRF versus IFN

After restriction and weighting of DRF-treated patients in EVOLVE-MS-1 to match the average baseline characteristics of IFN-treated patients in RADIANCE, the ARR was lower in DRF-treated patients 0.18 (95% CI: 0.14–0.22) than IFN-treated patients 0.28 (95% CI: 0.23–0.32) with a rate difference of -0.10 (95% CI: -0.16 to -0.04) ([Figure 2](#)). Compared with IFN, a lower proportion of DRF-treated patients had CDP sustained for 12 weeks (risk difference, -5.1% [95% CI: -9.2% to -1.5%]), but there was not strong evidence favoring DRF over IFN for 24-week CDP (risk difference, -2.2% [95% CI: -5.5% to 0.94%]) ([Table 2](#); [Figure 3](#)). Approximately 76.4% (95% CI: 71.8%–81.2%) of DRF-treated patients did not have Gd+ T1 lesions compared with 56.2% (95% CI: 51.6%–60.9%) of IFN-treated patients ([Figure 4](#)). Similarly, a higher proportion of DRF-treated patients were without new/newly enlarging T2 lesions compared with IFN-treated patients (31.7% [95% CI: 27.0%–36.5%] in DRF-treated patients and 18.4% [95% CI: 14.8%–22.0%] in IFN-treated patients, respectively).

Sensitivity analysis to account for differences in duration of follow-up

We conducted a sensitivity analysis to estimate radiological outcomes in EVOLVE-MS-1 at a hypothetical week 104, to match the duration of the RADIANCE study. [Supplementary Table 2](#) shows the results of this sensitivity analysis. If EVOLVE-MS-1 had an additional 8 weeks of follow-up, the expected proportions of patients without Gd+ T1 lesions was 75.1% (95% CI: 69.8%–80.8%) and without new/newly enlarging T2 lesions was 26.2% (95% CI: 20.5%–32.4%) in the comparison of DRF versus OZA. Similar findings were observed in the comparison of DRF versus IFN ([Supplementary Table 2](#)). Although these results indicate that there would have been a decreasing proportion of patients free of these lesions if there was longer follow-up in EVOLVE-MS-1, the results remain favorable for DRF compared with OZA and IFN.

Sensitivity analysis to compare outcomes in newly enrolled patients

We also conducted a sensitivity analysis that compared outcomes for efficacy analyses in the subset of newly enrolled patients in EVOLVE-MS-1, therefore excluding patients who had previously participated in the EVOLVE-MS-2 study. Balance was achieved across baseline characteristics between newly enrolled DRF-treated patients in

Table 2. Comparison of outcomes after restriction and matching-adjusted indirect comparison weightings.

	RADIANCE [†]		EVOLVE-MS-1		DRF vs OZA		DRF vs IFNβ-1a		
	OZA 1 mg	IFNβ-1a 30 µg	DRF restricted sample	EVOLVE-MS-1, DRF, weighted	Weighted rate/risk difference [‡]	Weighted rate/risk ratio [‡]	EVOLVE-MS-1, DRF, weighted	Weighted rate/risk difference [‡]	Weighted rate/risk ratio [‡]
ARR [§] (95% CI)	n = 433 0.17 (0.14 to 0.21)	n = 441 0.28 (0.23 to 0.32)	n = 460 0.19 (0.16 to 0.22)	ESS = 298 0.18 (0.14 to 0.22)	0.01 (-0.04 to 0.06)	1.1 (0.71 to 1.4)	ESS = 298 0.18 (0.14 to 0.22)	-0.10 (-0.16 to -0.04)	0.65 (0.44 to 0.82)
Proportion of patients with disability progression for 12 weeks, % (95% CI)	n = 433 12.5 (9.5 to 15.7)	n = 441 11.3 (8.4 to 14.3)	n = 452 10.3 (7.5 to 13.1) [¶]	ESS = 294 6.1 (3.5 to 8.5) [¶]	-6.4 (-10.3 to -2.4) [¶]	0.49 (0.21 to 0.71) [¶]	ESS = 295 6.2 (3.5 to 8.6) [¶]	-5.1 (-9.2 to -1.5) [¶]	0.56 (0.22 to 0.78) [¶]
Proportion of patients with disability progression for 24 weeks, % (95% CI)	n = 433 9.7 (6.9 to 12.5)	n = 441 6.6 (4.3 to 9.1)	n = 452 7.3 (5.1 to 9.7) [¶]	ESS = 294 4.5 (2.2 to 6.6) [¶]	-5.1 (-8.9 to -1.6) [¶]	0.48 (0.14 to 0.72) [¶]	ESS = 295 4.4 (2.1 to 6.4) [¶]	-2.2 (-5.5 to 0.94) [¶]	0.69 (0.15 to 1.1) [¶]
Absence of Gd+ T1 lesions, % (95% CI)	n = 433 [#] 65.6 (61.1 to 70.1)	n = 441 [#] 56.2 (51.6 to 60.9)	n = 452 70.8 (66.6 to 75.0) ^{††}	ESS = 294 77.6 (73.0 to 82.3) ^{††}	12.0 (5.3 to 18.7) ^{††}	1.2 (1.1 to 1.3) ^{††}	ESS = 295 76.4 (71.8 to 81.2) ^{††}	20.2 (13.4 to 27.1) ^{††}	1.4 (1.2 to 1.5) ^{††}
Absence of new/newly enlarging T2 lesions, % (95% CI)	n = 433 [#] 23.8 (19.8 to 27.8)	n = 441 [#] 18.4 (14.8 to 22.0)	n = 452 33.6 (29.4 to 38.1) ^{††}	ESS = 294 33.6 (28.8 to 38.7) ^{††}	9.8 (0.22 to 19.2) ^{††}	1.4 (0.94 to 1.8) ^{††}	ESS = 295 31.7 (27.0 to 36.5) ^{††}	13.3 (3.7 to 22.6) ^{††}	1.7 (1.2 to 2.3) ^{††}

[†]Data on outcomes in RADIANCE were obtained from Cohen et al. [24].

[‡]Weighted incidence rate differences and incidence rate ratios are presented for ARR. Weighted risk differences and risk ratios are presented for the outcomes of 12- and 24-week CDP, absence of Gd+ T1 lesions and absence of new/newly enlarging T2 lesions.

[§]ARR was analyzed using Poisson regression and included the natural log transformation of time on study as an offset term.

[¶]RADIANCE's definition of CDP was applied to EVOLVE-MS-1. Progression of disability that sustained for 12 weeks or 24 weeks was defined by ≥1.0 point from baseline EDSS.

[#]Cohen et al. [24] did not report the number of patients with data available for the outcomes of absence of Gd+ T1 lesions and absence of new/newly enlarging T2 lesions. However, it can be assumed that the overall number of patients analyzed was 433 in the ozanimod 1.0-mg arm and 441 in the IFN arm since non-responder imputation was used to account for patients missing 2-year MRI data in RADIANCE [24]. Non-responder imputation involves imputing patients missing MRI data as not being lesion-free.

^{††}Non-responder imputation was used to address missing data, consistent with approach used to analyze this outcome in RADIANCE.

Bootstrapping was used to obtain CIs around the weighted estimates to account for uncertainty in the sampling error and uncertainty in the weights.

ARR: Annualized relapse rate; CDP: Confirmed disability progression; CI: Confidence interval; DRF: Diroximel fumarate; EDSS: Expanded Disability Status Scale; ESS: Effective sample size; Gd+: Gadolinium-enhancing; IFNβ-1a: Interferon beta-1a; MS: Multiple sclerosis; OZA: Ozanimod; SD: Standard deviation.

EVOLVE-MS-1 and the OZA and IFN arms of RADIANCE after restriction and weighting (Supplementary Table 3). Clinical and radiological outcomes after restriction and weighting in newly enrolled EVOLVE-MS-1 patients were similar to those for the full population after restriction and weighting (Supplementary Table 4). Therefore, comparisons versus the OZA and IFN arms of the RADIANCE study were generally consistent with those from the primary MAIC analyses.

Discussion

Several DMTs are now available for the treatment of RRMS, offering different routes of administration, dosing schedules and efficacy and safety profiles. For more recently approved DMTs such as DRF, there are few studies that have directly compared their efficacy with that of other DMTs, although the efficacy and safety profile of DRF is expected to be similar to that of DMF, due to their bioequivalence in producing the active metabolite MMF. MAIC can be used to evaluate the comparative efficacy of DMTs in the absence of randomized head-to-head trials. Our analyses used clinical trial data from two separate clinical trials, EVOLVE-MS-1 and RADIANCE, to evaluate the comparative efficacy of DRF, OZA and IFN. We used MAICs to compare clinical and radiological outcomes for DRF from the EVOLVE-MS-1 study with those for OZA and IFN from the RADIANCE study. No significant differences were observed between the ARR for DRF and OZA; however, 12- and 24-week CDP and radiological outcomes favored DRF over OZA. All clinical and radiological outcomes favored DRF versus IFN, with the exception of 24-week CDP, for which there was not strong evidence favoring DRF. These results are consistent with findings from earlier real-world comparisons of DMF and IFN, which indicated more favorable

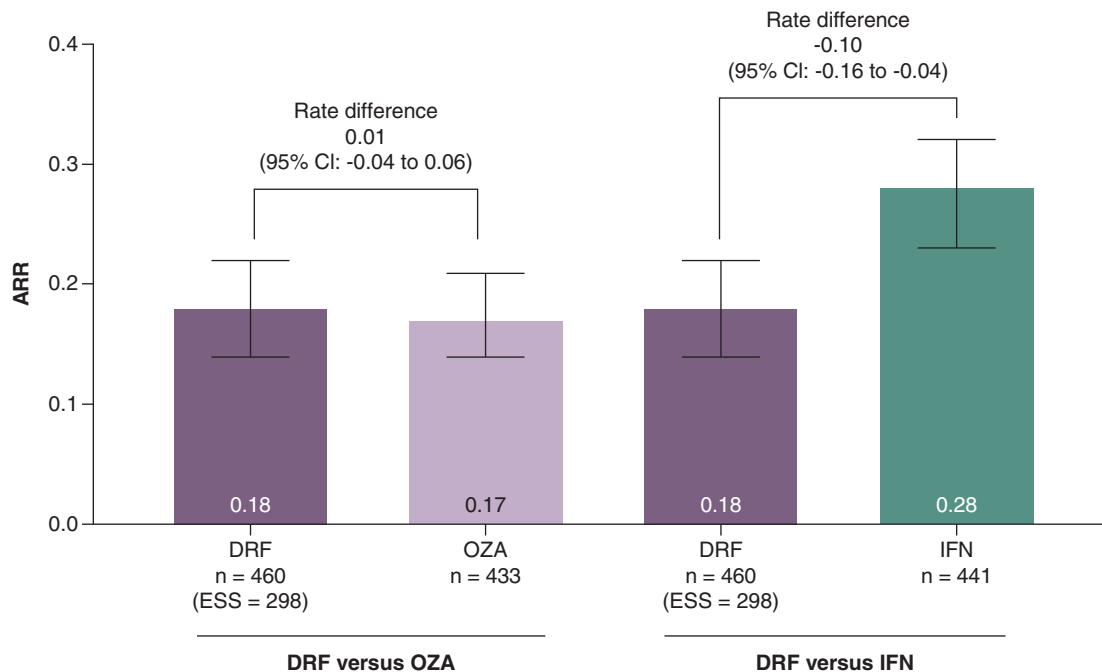


Figure 2. Annualized relapse rate for diroxime fumarate versus ozanimod and diroxime fumarate versus interferon beta-1a after matching-analysis indirect comparison weighting. ARR was analyzed using Poisson regression and included the natural log transformation of time on study as an offset term. Negative rate differences for ARR indicate favorable outcomes for DRF. Data on ARR outcomes in RADIANCE were obtained from Cohen *et al.* [24].

ARR: Annualized relapse rate; CI: Confidence interval; DRF: Diroxime fumarate; ESS: Effective sample size; IFN: Interferon beta-1a; MAIC: Matching-analysis indirect comparison; OZA: Ozanimod.

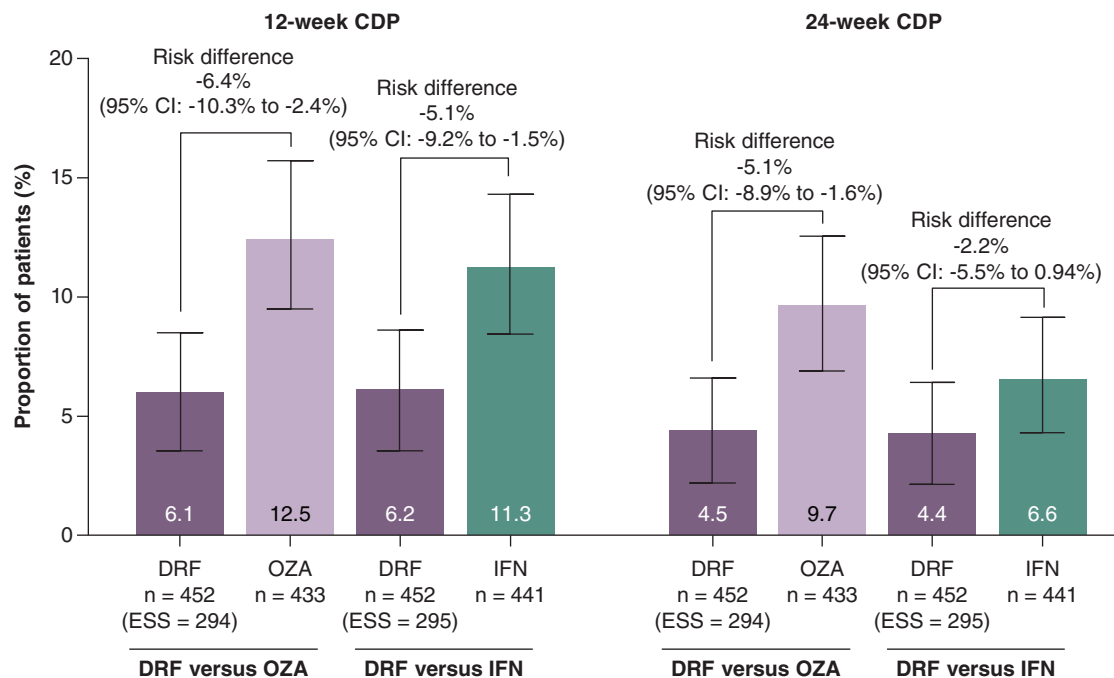


Figure 3. Twelve- and 24-week confirmed disability progression for diroxime fumarate versus ozanimod and diroxime fumarate versus interferon beta-1a after matching-analysis indirect comparison weighting. RADIANCE's definition of CDP was applied to EVOLVE-MS-1. Progression of disability that sustained for 12 weeks or 24 weeks was defined by ≥ 1.0 point from baseline EDSS. Data on CDP outcomes in RADIANCE were obtained from Cohen *et al.* [24]. CDP: Confirmed disability progression; CI: Confidence interval; DRF: Diroxime fumarate; EDSS: Expanded Disability Status Scale; ESS: Effective sample size; IFN: Interferon beta-1a; OZA: Ozanimod.

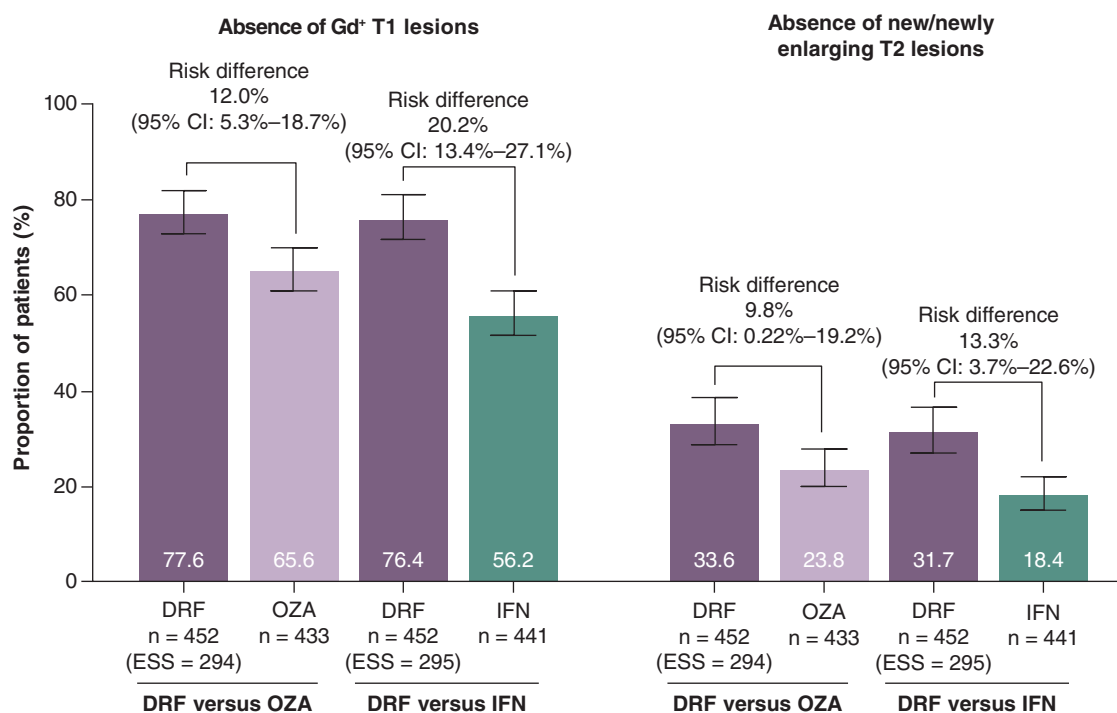


Figure 4. Absence of Gd+ T1 lesions and new/newly enlarging T2 lesions for diroximel fumarate versus ozanimod and diroximel fumarate versus interferon beta-1a after matching-analysis indirect comparison weighting. Non-responder imputation was used to address missing data, consistent with approach used to analyze this outcome in RADIANCE. Data on radiological outcomes in RADIANCE were obtained from Cohen et al. [24]. CI: Confidence interval; DRF: Diroximel fumarate; ESS: Effective sample size; IFN: Interferon beta-1a; OZA: Ozanimod.

relapse and disability outcomes for DMF [18,32], and the RADIANCE study, in which IFN and OZA had similar disability outcomes [24].

A similar methodological approach was used for an earlier MAIC that evaluated the comparative efficacy of DRF versus ponesimod (PON), another drug from the same S1PRM class as OZA [22]. The MAIC used IPD from EVOLVE-MS-1 and aggregate data from OPTIMUM, a 2-year, double-blind, phase III trial comparing PON and teriflunomide [22]. After MAIC weighting, DRF and PON had similar clinical efficacy, but DRF treatment was associated with a higher proportion of patients free from Gd+ T1 lesions versus PON [22].

Previous studies have also provided comparative effectiveness data for DMF and S1PRMs (e.g., fingolimod, ozanimod) using MAIC. A MAIC of DMF (DEFINE/CONFIRM trials) and fingolimod (FREEDOMS/FREEDOMS II trials) found that they had similar ARR, proportion of patients with 12-week CDP and proportion of patients with no evidence of disease activity [33]. In another MAIC of OZA (SUNBEAM and RADIANCE Part B trials) and DMF (DEFINE/CONFIRM trials), OZA appeared to have more favorable ARR and CDP outcomes than DMF [34]. This is in contrast with our current findings, which indicate that DRF and OZA have similar ARRs and that DRF is associated with improved CDP outcomes. It should be noted that SUNBEAM/RADIANCE Part B and DEFINE/CONFIRM were conducted at different times and used different MS diagnosis criteria, therefore making comparisons between them challenging. For example, the OZA trials required an MS diagnosis based on the revised 2010 McDonald criteria, while the DMF studies required an MS diagnosis based on 2005 McDonald criteria [34]. The newer version of the McDonald criteria allows for earlier diagnosis of cases, and therefore patients in newer trials may be younger and present with lower disease activity and slower clinical progression than patients in older trials using previous versions of the McDonald criteria [35,36]. This source bias could have disadvantaged DMF in the MAIC of OZA and DMF [34].

Our indirect comparison of the EVOLVE-MS-1 and RADIANCE studies has several limitations. First, there is the possibility of potential residual confounding due to the different study designs. The absence of a common comparator between EVOLVE-MS-1 and RADIANCE meant that an anchored MAIC of the two studies was not possible and therefore we could not assess residual confounding after MAIC weighting. A second limitation

is that the duration of RADIANCE was longer than that of EVOLVE-MS-1, which may have had an impact on radiological outcomes, since week 96 MRI assessments from EVOLVE-MS-1 were compared with week 104 MRI assessments from RADIANCE. To address this, sensitivity analyses were conducted to estimate the corresponding outcomes for EVOLVE-MS-1 at week 104, and these supported the outcomes from the initial MAIC analysis. A third potential limitation is that a number of patients in EVOLVE-MS-1 had rolled over from EVOLVE-MS-2 and were 're-baselined', which could have inflated the proportion of patients on DRF who were considered lesion-free at baseline. However, given the short duration of EVOLVE-MS-2, it was not expected that these patients would have a substantial effect on the outcomes of these analyses, and the primary analysis of EVOLVE-MS-1 had also included these patients who had rolled over from EVOLVE-MS-2 [25]. Omitting these patients from the primary analysis reported here would have resulted in a reduced sample size, and therefore these patients were retained. A sensitivity analysis restricted to only those patients who had newly enrolled into EVOLVE-MS-1 indicated that outcomes were consistent with those from the primary MAIC analysis, demonstrating that the inclusion of EVOLVE-MS-2 rollover patients in the primary analysis did not greatly influence the outcomes. As reported previously, discontinuations over the 5-week duration of EVOLVE-MS-2 were low (DRF: $n = 8$ [3.2%]; DMF: $n = 18$ [7.2%]) [14]. Fourth, as EVOLVE-MS-1 was a single-arm trial of DRF, there was no blinding of the assessor and patient to the treatment assignment. This could have led to underestimation of relapses and disability progression among DRF-treated patients, though MRI outcomes may be less impacted by lack of blinding. Fifth, we used non-responder imputation to calculate the proportions of patients without Gd+ T1 lesions and new/newly enlarging T2 lesions to be consistent with the approach used in RADIANCE [24], which is known to be a conservative method. Among the EVOLVE-MS-1 sample restricted to those who met the inclusion/exclusion criteria of RADIANCE, there were 104 patients missing data on Gd+ T1 lesions and 103 missing data on new/newly enlarging T2 lesions at week 96. We assumed that they all developed lesions with the non-responder imputation approach. In EVOLVE-MS-1, there were a total of 247 (24.3%) discontinuations among patients on DRF [25], and in RADIANCE, 45 (10.4%) patients on OZA 1 mg and 65 (14.7%) patients on IFN beta-1a 30 µg discontinued treatment [24]; differences in study design (open-label vs double-blind, respectively) should be kept in mind when evaluating discontinuation rates. Sixth, our analysis to account for differences in follow-up time between the trials assumes a constant incidence rate over the time period, with no competing risks, and that the risk is low. Violations to these assumptions may lead to biased risk estimates. Finally, no safety data were included in the MAICs reported here.

Conclusion

These indirect comparisons of DRF with OZA and IFN contribute to the burgeoning literature on of the comparative efficacy of fumarates with other DMTs. These analyses indicate that disability progression and radiological outcomes were favorable for DRF versus OZA, although no significant differences were observed in ARR. All clinical and radiological outcomes favored DRF versus IFN, except for 24-week CDP. These findings may further support similar efficacy between the fumarate and S1PRM class and better efficacy of fumarates over interferons. Such outcomes may be valuable in the consideration of treatment options for MS, for example by supporting treatment decisions made by patients and clinicians, and informing the assessments made by reimbursement bodies and regulatory agencies.

Summary points

- Diroximel fumarate (DRF), ozanimod (OZA) and interferon beta-1a (IFN) are disease-modifying therapies (DMTs) approved for the treatment of relapsing forms of multiple sclerosis (MS).
- Comparisons of the efficacy of DRF versus OZA and IFN would be valuable to patients and clinicians in making informed treatment decisions. However, no randomized, controlled trials have directly compared DRF versus OZA or IFN.
- Matching-adjusted indirect comparisons (MAICs) can be used to adjust for cross-trial differences and compare the efficacy of DMTs evaluated in separate studies.
- This analysis used MAICs to compare outcomes from the 2-year, open-label, single-arm, phase III EVOLVE-MS-1 study of DRF (NCT02634307) and the 2-year, double-blind, phase III RADIANCE study of OZA and intramuscular IFN beta-1a (NCT02047734).
- Comparisons between DRF and OZA indicated that disability progression and radiological outcomes were favorable for DRF, while no differences were observed in annualized relapse rates for the two DMTs.
- In comparisons of DRF and IFN, all clinical and radiological outcomes favored DRF, with the exception of 24-week confirmed disability progression, for which there was not strong evidence favoring DRF.
- Limitations include potential residual confounding due to different study designs and populations, and the use of unanchored MAIC since there was no common comparator between the two trials.
- These findings may be informative for patients and clinicians when considering different treatment options for MS.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at:
<https://bpl-prod.literatumonline.com/doi/10.57264/cer-2023-0161>

Author contributions

T Jiang: study conception, study design, data analysis, reviewed and revised drafts of the manuscript and approved the final version. M Shanmugasundaram: study design, data analysis, reviewed and revised drafts of the manuscript and approved the final version. I Božin: study conception, study design, data analysis, reviewed and revised drafts of the manuscript and approved the final version. MS Freedman: reviewed and revised drafts of the manuscript and approved the final version. JB Lewin: study design, data analysis, reviewed and revised drafts of the manuscript and approved the final version. C Shen: study design, data analysis, reviewed and revised drafts of the manuscript and approved the final version. T Ziemssen: reviewed and revised drafts of the manuscript and approved the final version. DL Arnold: reviewed and revised drafts of the manuscript and approved the final version.

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Competing interests disclosure

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Ethical conduct of research

Ethical approval was not applicable for this analysis as data were based on existing outputs from the EVOLVE-MS-1 and RADIANCE studies.

Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been published previously [24,25].

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