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Relapse-Related Outcomes in Patients With Multiple Sclerosis Treated With First-Line Disease-Modifying Therapies

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INTRODUCTION/BACKGROUND

- Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that is characterized by inflammation and demyelination of the CNS, potentially causing severe physical and mental disability.[1]
- The most prevalent subtype of MS is relapsing-remitting multiple sclerosis (RRMS), which accounts for 85% of all cases.[2]
- The mainstay of MS treatment is disease-modifying therapies (DMTs), which target the process leading to relapses and disease progression. These include platform therapies (interferons and glatiramer acetate), oral agents (fingolimod, dimethyl fumarate, teriflunomide), and infusion therapies (natalizumab, ocrelizumab, alemtuzumab).[3,4]
- This study compared the time to first relapse, annualized relapse rates (ARRs), and risk of relapse in patients with RRMS on oral vs platform DMTs in a first-line setting.

METHODS

Study Design

- This is a retrospective cohort study using patient-level data from the IBM MarketScan Commercial and Medicare Supplemental databases (IBM Watson Health, Cambridge, MA), with observational periods from January 1, 2011 through December 31, 2017.

Key Inclusion Criteria

- At least 1 claim for a DMT anytime in the database. The earliest DMTs treatment date was defined as the study index date.
- At least 1-year pre- and post-index continuous enrollment (31-day gap allowance) with medical and pharmacy coverage.
- At least 1 claim for MS diagnosis (ICD-9-CM 340.XX or ICD-10-CM G35.XX) any time prior to or within 30 days after index date during the continuous enrollment period.

Key Exclusion Criteria

- <18 years old on index date
- Missing birth year or gender
- Patients treated with multiple DMTs on their index date

Study Outcomes

- **ARR:** calculated as the number of relapse episodes that a patient had after treatment initiation (not based on calendar year) divided by the total person years during the period of interest.
- **First-line therapy:** treatment defined by index DMT treatment; patients were considered to be on continuous therapy until the day before new DMT is initiated or end of study time frame was reached.
- **Relapse:** ≥1 hospitalization with a principal diagnosis of MS or ≥1 outpatient visit with an MS diagnosis followed by a claim for an oral or IV corticosteroid within 7 days.[5] A "clean period" of 30 days with none of the events described above is required between the start of separate relapses.

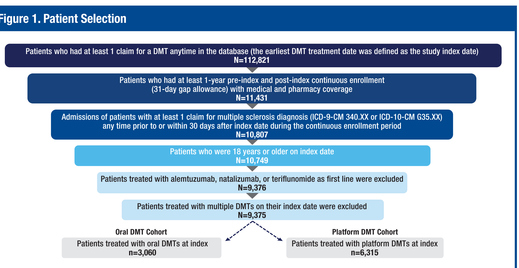
Data Analysis

- Patients were stratified by the DMT route of administration:
  - Oral (fingolimod, dimethyl fumarate)
  - Platform (interferon beta-1a, interferon beta-1b, glatiramer acetate, peginterferon beta-1a)
- Relapse rates (ARRs) were annualized for the first 3 years post-index.
- Descriptive statistics were reported for baseline demographics and other outcomes for each treatment cohort. Continuous variables were summarized using mean, standard deviation, median, IQR, Q1 and Q3. For categorical variables, counts and percentages of patients were provided. T tests and chi-square (or Fisher's exact for sample size < 5) tests were used to compare continuous and categorical variables, respectively.
- Generalized linear models were used to compare ARRs, and Cox regression was used to estimate the risk of relapse after adjusting for age, gender, index year, Charlson Comorbidity Index (CCI) score, baseline relapse, and time from earliest MS diagnosis to first-line DMT.

RESULTS

- A total of 9,375 patients with MS met the study selection criteria; 3,060 patients were treated with first-line oral DMTs and 6,315 were treated with first-line platform DMTs (**Figure 1**).
- Descriptive demographics are shown in **Table 1**.

Figure 1. Patient Selection



DMT, disease-modifying therapy.

Table 1. Baseline Demographics and Clinical Characteristics

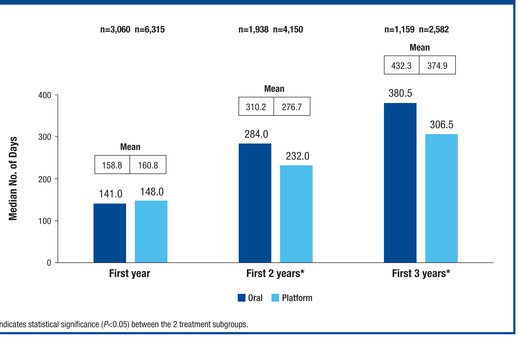
	All Patients		Patients Treated with Oral DMT at Index		Patients Treated with Platform DMT at Index		*P*-value
Characteristic	N	%	N	%	N	%	
Cohort	9,375	100.00	3,060	100.00	6,315	100.00	
Age at index (years)							
Mean (SD)	44.7 (11.5)		45.17 (11.08)		44.47 (11.7)		0.0069*
Median (Q1, Q3)	45 (36, 53)		45 (37, 53)		44 (36, 53)		
Sex							
Male	2,249	24.00	776	25.40	1,473	23.30	0.306*
Female	7,126	76.00	2,284	74.60	4,842	76.70	
Region							
Northeast	2,022	21.6	676	22.1	1,346	21.3	0.9124
North Central	2,130	22.7	685	22.4	1,445	22.9	
South	3,530	37.7	1,154	37.7	2,376	37.6	
West	1,608	17.2	517	16.9	1,091	17.3	
Unknown	85	0.9	28	0.9	57	0.9	
CCI Score							
Mean (SD)	0.70 (1.25)		0.65 (1.19)		0.73 (1.28)		0.0033*
Comorbid Conditions							
Infections	1,641	17.50	498	16.27	1,143	18.10	0.0292*
Depression	1,010	10.77	339	11.08	671	10.63	0.5072
Cardiac arrhythmia	522	5.57	205	6.70	317	5.02	0.0002*
Glaucoma	454	4.84	161	5.26	293	4.64	0.1886
Seizure	260	2.77	82	2.68	178	2.82	0.7009
Liver injury	145	1.55	56	1.83	89	1.41	0.1216
Leukopenia	41	0.44	16	0.52	25	0.40	0.3823
Ophthalmologic (macular edema)	37	0.39	23	0.75	14	0.22	0.0001*
Neutropenia	26	0.28	11	0.36	15	0.24	0.2924
Angioedema	18	0.19	4	0.13	14	0.22	0.3454
Anaphylaxis	17	0.18	2	0.07	15	0.24	0.0662

*Indicates statistical significance (*P*<0.05) between the 2 treatment subgroups.
DMT, disease modifying therapy; SD, standard deviation.

RESULTS (cont'd)

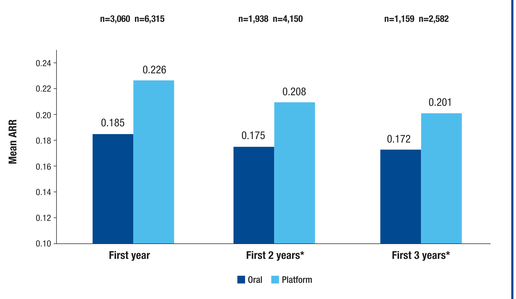
- Patients treated with oral DMTs had significantly longer time to first relapse compared with those on platform therapy within the first 3 years (median 380.5 vs 306.5 days, *P*=0.0054, respectively) (**Figure 2**).
- Patients treated with oral DMTs had significantly lower ARRs than those treated with platform DMTs (year 1 post-index: 0.226 vs 0.185, *P*<0.0001; years 1–2: 0.208 vs 0.175, *P*<0.0001; years 1–3: 0.201 vs 0.172, *P*<0.0001) (**Figure 3**).
- Similar results were obtained after controlling for covariates (**Figure 4**).
- First-line oral DMT patients had a reduced risk of experiencing relapse compared with first-line platform patients, see **Table 2** (year 1: HR=0.822, *P*<0.0001; years 1–2: HR=0.848, *P*<0.0001; years 1–3: HR=0.841, *P*<0.0001).

Figure 2. Unadjusted Time to First Relapse on First-Line MS Therapy



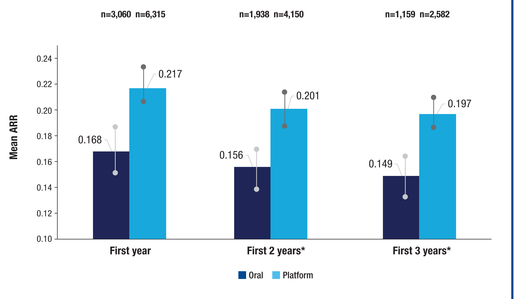
*Indicates statistical significance (*P*<0.05) between the 2 treatment subgroups.

Figure 3. Unadjusted ARR on First-Line MS Therapy



*Indicates statistical significance (*P*<0.05) between the 2 treatment subgroups.
ARR, annualized relapse rate.

Figure 4. Adjusted ARR on First-Line MS Therapy



*Indicates statistical significance (*P*<0.05) between the 2 treatment subgroups.
ARR, annualized relapse rate.

Table 2. Risk of First Relapse on First-Line MS Therapy by Cox Proportional Hazard Model

	Oral vs Platform (reference)			
Time to first relapse	HR	Lower 95% CI	Upper 95% CI	*P*-value
First year	0.822	0.730	0.926	0.0012
First 2 years	0.848	0.752	0.957	0.0075
First 3 years	0.841	0.731	0.967	0.0153

CI, confidence interval; HR, hazard ratio; MS, multiple sclerosis.

CONCLUSIONS

- Time to first relapse was significantly longer in patients taking oral therapies than those taking platform therapies.
- Patients newly treated with oral DMTs had lower relapse rates compared with platform therapies across the study period.
- Patients treated with oral therapies also had a reduced risk of relapse compared with those treated with platform therapies.

These findings suggest that initiating patients with oral therapies may result in improved relapse outcomes compared with platform therapies.

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DISCLOSURES

SC: Biogen, Novartis, Pear Therapeutics, Roche Genentech, Celgene Corporation, and Sanofi Genzyme – advisory board; Biogen, Novartis, Roche Genentech, and Sanofi Genzyme – speaker; AbbVie, Adamas, Althios, Biogen, EMD Serono, MedDay, NARCRMS, Novartis, Providence St. Vincent Foundation, Roche Genentech, and Sanofi Genzyme – grant/research support. **FC, DO, JHH, & WW:** Genesis Research – employment (Genesis Research provides consulting services to Celgene Corporation). **TT:** Celgene Corporation – employment.

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