Relapse rates of patients with multiple sclerosis newly initiating subcutaneous interferon β-1a vs oral disease-modifying drugs in the real world

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Introduction

- Disease-modifying drugs (DMDs) have been shown to be efficacious in reducing relapse frequency in multiple sclerosis (MS).
- Randomized controlled trials remain the gold standard for assessing the efficacy of treatments; however, they may be inadequate for addressing questions about the 'real-world' effectiveness and safety of these interventions.[1]
- The Institute of Medicine defines comparative effectiveness as "the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in 'real-world' settings."[2]
- Administrative healthcare claims databases provide the ability to assess comparative effectiveness and safety of DMDs for MS in a real-world setting reflective of clinical practice in a large number of patients.[3,4]
- Self-injectable DMDs have historically been the most commonly used DMDs. In recent years, newer DMDs, including oral formulations (ie, dimethyl fumarate, fingolimod, and teriflunomide), have been approved. However, there is limited real-world evidence (RWE) for the estimated comparative effectiveness of oral DMDs.
  - No published RWE studies directly comparing subcutaneous interferon beta-1a (scIFNβ1a) with oral DMDs were identified in the published literature.
  - Existing studies have often combined scIFNβ1a with other interferons and/or with glatiramer acetate.[5,6]

Objective

- To utilize real-world data to evaluate relapse rates of patients with MS newly initiating scIFNβ1a versus oral DMDs (ie, dimethyl fumarate, fingolimod, and teriflunomide).

Methods

Data source

- This was a retrospective database study using IMS Health Real World Data (RWD) Adjudicated Claims – US data from January 1, 2012 to June 30, 2013.
- The IMS RWD Adjudicated Claims – US database is an anonymous, HIPAA-compliant, national managed care database that represents approximately 70 million enrollees from over 65 health plans.
- IMS RWD Adjudicated Claims – US data include demographic variables (age, sex, region of the US), eligibility by month, healthcare resource use, and the adjudicated payment for inpatient, outpatient, and pharmaceutical services.

Patient population

- Inclusion criteria selected patients who were between 18 and 65 years of age at the time of DMD initiation or during the period of observation (65 years of age represents the most frequent age for transition to Medicare), with at least one medical claim with a diagnosis for MS (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code = 340.xx) and at least one prescription for scIFNβ1a, dimethyl fumarate, fingolimod, or teriflunomide after MS diagnosis between January 1, 2012 and June 30, 2013.
- The date of the first DMD prescription was the index date.
- In order to examine patients new to treatment (treatment naïve), any patient with a DMD during the 12 months prior to the index date was excluded.
- Included patients had continuous eligibility for the 12 months before and 12 months after the index date.

DMD treatment outcomes – relapses

- Relapse was assessed 12 months following DMD initiation using definitions of relapse similar to those used in previously published retrospective database evaluations[3,4]:
  - MS-related hospitalization
  - MS-related emergency room (ER) visit, or
  - MS-related outpatient visit with corticosteroid prescription ±7 days.

Descriptive/univariate analyses

- Baseline demographic and clinical characteristics were compared among scIFNβ1a and oral DMD cohorts (ie, dimethyl fumarate, fingolimod, and teriflunomide).
- For descriptive (ie, unadjusted) analyses, categorical variables were summarized using frequencies and percentages; continuous variables were summarized using means (with confidence intervals), standard deviations, and medians.
- Pairwise Chi-square tests were conducted using scIFNβ1a as the reference group (ie, all pairwise comparison with scIFNβ1a). Continuous variables were tested with *t*-tests using scIFNβ1a as the reference group.

Multivariable analyses

- Logistic regression was used to evaluate the likelihood of relapse (ie, MS-related hospitalization, MS-related ER visit, or MS-related outpatient visit with corticosteroid prescription ±7 days) with scIFNβ1a versus dimethyl fumarate, fingolimod, or teriflunomide.
- Covariates included patient demographics (ie, age, sex, region) and clinically meaningful measures of disease severity (ie, 90-day pre-index indicators for relapse, neurologist/established patient visits, and magnetic resonance imaging [MRI]).
  - 90 days was selected as a time period that would be likely to have utilization that was associated with the initiation of DMD therapy.
- Models were evaluated for interactions with each individual DMD treatment. Odds ratios and confidence intervals for the odds of having a relapse are reported.

Results

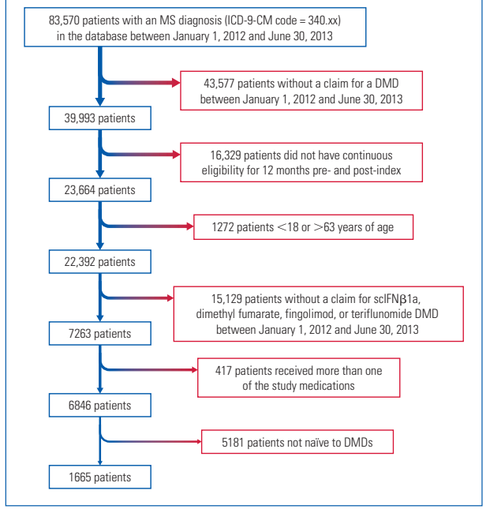
Patient selection

- A total of 1665 patients (686 scIFNβ1a, 406 dimethyl fumarate, 455 fingolimod, and 118 teriflunomide) met the inclusion criteria (**Figure 1**).

Baseline characteristics

- Baseline patient demographic and clinical characteristics for the treatment cohorts are shown in **Table 1**.
  - Patients initiating scIFNβ1a were statistically significantly younger compared with patients initiating oral DMDs.
  - A significantly greater proportion of patients initiating scIFNβ1a were from the Midwest compared with patients initiating teriflunomide. A significantly greater proportion of patients initiating dimethyl fumarate and teriflunomide were from the Northeast compared with patients initiating scIFNβ1a. A significantly greater proportion of patients initiating dimethyl fumarate were from the West and a significantly lower proportion were from the South compared with scIFNβ1a patients.
  - Patients initiating scIFNβ1a had a significantly lower comorbidity score during the year prior to initiating treatment compared with patients initiating dimethyl fumarate.
  - A significantly smaller proportion of patients initiating scIFNβ1a had: depression or gastrointestinal disease compared with patients initiating oral agents; arthritis or thyroid disease compared with patients initiating teriflunomide; and anxiety compared with patients initiating dimethyl fumarate.

Figure 1. Patient selection flowchart.



DMD, disease-modifying drug; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; MS, multiple sclerosis; scIFNβ1a, subcutaneous interferon beta-1a.

Table 1. Baseline demographic and clinical characteristics of patients with MS newly initiating scIFNβ1a, dimethyl fumarate, fingolimod, or teriflunomide.

Characteristic	scIFNβ1a	Dimethyl fumarate	Fingolimod	Teriflunomide
n	686	406	455	118
Age, years, mean (SD)	42.1 (10.3)	**46.4 (9.8)****	**45.2 (9.6)****	**48.2 (7.3)****
Female, n (%)	516 (75.2)	312 (76.8)	336 (73.8)	93 (78.8)
Region, n (%)				
Northeast	176 (25.7)	**131 (32.3)***	115 (25.3)	**44 (37.3)***
Midwest	263 (38.3)	135 (33.3)	152 (33.4)	**33 (28.0)***
South	207 (30.2)	**96 (23.6)***	162 (35.6)	32 (27.1)
West	40 (5.8)	**44 (10.8)****	26 (5.7)	9 (7.6)
CCI score, mean (SD)	0.54 (1.13)	**0.70 (1.28)***	0.43 (0.85)	0.58 (0.88)
Select comorbidities, n (%)				
Anxiety	66 (9.6)	**67 (16.5)****	50 (11.0)	17 (14.4)
Arthritis (RA/OA)	40 (5.8)	30 (7.4)	26 (5.7)	**15 (12.7)***
Depression	86 (12.5)	**89 (21.9)****	**82 (18.0)***	**25 (21.2)***
Diabetes	45 (6.6)	36 (8.9)	29 (6.4)	8 (6.8)
Gastrointestinal disease[a]	91 (13.3)	**87 (21.4)****	**86 (18.9)***	**27 (22.9)***
Hypertension	137 (20.0)	92 (22.7)	100 (22.0)	26 (22.0)
Thyroid disease	94 (13.7)	71 (17.5)	68 (14.9)	**27 (22.9)***

Bolded values denote significant differences.

CCI, Charlson Comorbidity Index; MS, multiple sclerosis; OA, osteoarthritis; RA, rheumatoid arthritis; scIFNβ1a, subcutaneous interferon beta-1a; SD, standard deviation.

[a]Including constipation, diarrhea, dysphagia, gastroesophageal reflux disease, and irritable bowel syndrome.

*p<0.05 using pairwise Chi-square test or independent sample *t*-test versus scIFNβ1a as the standard (no adjustment for multiplicity); **p<0.005 using pairwise Chi-square test or independent sample *t*-test versus scIFNβ1a as the standard (no adjustment for multiplicity).

- Clinically meaningful measures of patient baseline severity are presented in **Table 2**.
  - A significantly greater proportion of patients initiating scIFNβ1a had 90-day pre-index relapses compared with patients initiating fingolimod.
  - A significantly greater proportion of patients initiating dimethyl fumarate had 90-day pre-index neurologist/established patient visits compared with patients initiating scIFNβ1a.
  - A significantly greater proportion of patients initiating scIFNβ1a had 90-day pre-index MRIs compared with patients initiating fingolimod and teriflunomide.

Table 2. Clinically meaningful measures of patient baseline severity: 90-day pre-index relapses, neurologist/established patient visits, and MRIs.

Characteristic	scIFNβ1a	Dimethyl fumarate	Fingolimod	Teriflunomide
n	686	406	455	118
90-day pre-index relapses, n (%)	204 (29.7)	105 (25.9)	**105 (23.1)***	34 (28.8)
90-day pre-index neurologist/ established patient visits, n (%)	532 (77.6)	**347 (85.5)****	352 (77.4)	97 (82.2)
90-day pre-index MRI, n (%)	317 (46.2)	163 (40.1)	**104 (22.9)****	**40 (33.9)***

Bolded values denote significant differences.

MRI, magnetic resonance imaging; scIFNβ1a, subcutaneous interferon beta-1a.

*p<0.05 using pairwise Chi-square test versus scIFNβ1a as the standard (no adjustment for multiplicity); **p<0.005 using pairwise Chi-square test versus scIFNβ1a as the standard (no adjustment for multiplicity).

DMD treatment outcomes – relapses

- Relapse rates during the first year on treatment for patients are presented in **Table 3**.
- There were no significant differences in 1-year unadjusted rates of MS-related inpatient stays or ER visits among the DMDs.
- The 1-year unadjusted rate of outpatient relapse was significantly higher in patients initiating dimethyl fumarate and teriflunomide compared with patients initiating scIFNβ1a.
- The 1-year unadjusted rate of any relapse was significantly greater in patients initiating dimethyl fumarate or teriflunomide compared with scIFNβ1a.

Table 3. Unadjusted rates of post-index relapses among treatment groups (MS–related inpatient stays, ER visits, and outpatient relapses).

Characteristic	scIFNβ1a	Dimethyl fumarate	Fingolimod	Teriflunomide
n	686	406	455	118
MS-related inpatient stay, n (%)	18 (2.6)	7 (1.7)	17 (3.7)	4 (3.4)
MS-related ER visit, n (%)	24 (3.5)	16 (3.9)	16 (3.5)	8 (6.8)
Outpatient relapse, n (%)	135 (19.7)	**109 (26.8)***	83 (18.2)	**38 (32.2)****
Any relapse, n (%)	149 (21.7)	**117 (28.8)***	96 (21.1)	**43 (36.4)****

Bolded values denote significant differences.

ER, emergency room; MS, multiple sclerosis; scIFNβ1a, subcutaneous interferon beta-1a.

*p<0.05 using pairwise Chi-square test versus scIFNβ1a as the standard (no adjustment for multiplicity); **p<0.005 using pairwise Chi-square test versus scIFNβ1a as the standard (no adjustment for multiplicity).

Multivariable analyses

- Factors predictive of relapse in the multivariable analyses are shown in **Table 4**.
  - After controlling for covariates, initiation of dimethyl fumarate or teriflunomide was associated with higher likelihood of relapse (odds ratio [OR] 1.5; p=0.0050 and OR 2.1; p=0.0006, respectively) relative to scIFNβ1a.
  - A neurologist/established patient visit (p=0.0335) and MS relapse (p<0.0001) in the 90 days pre-index were predictive of relapse.
- Patients with a relapse in the 90 days prior to DMD initiation had odds of relapse in the post-index period that were 2.3 times greater than patients without an indication of relapse in the 90 days pre-index.
- No interactions between the DMD treatment type and the other model variables were statistically significant.

Table 4. Logistic regression predicting odds of relapse resulting in inpatient, ER, or outpatient relapse.

Covariate	OR estimate	Lower 95% CI	Upper 95% CI	p value
Male (vs female)	1.183	0.903	1.561	0.2287
Age	1.153	0.712	1.916	0.9368
Region (vs West)				
East	1.157	0.721	1.911	0.9046
Midwest	1.280	0.793	2.124	0.2816
South	0.995	0.983	1.007	0.3997
Disease severity indicators				
90-day pre-index relapses	2.251	1.755	2.885	**<0.0001**
90-day pre-index neurologist/ established patient visits	1.401	1.032	1.925	**0.0335**
90-day pre-index MRI	0.838	0.653	1.071	0.1598
Oral DMD treatment (vs scIFNβ1a)				
Dimethyl fumarate	1.523	1.135	2.043	**0.0050**
Fingolimod	0.993	0.733	1.341	0.9647
Teriflunomide	2.129	1.373	3.273	**0.0006**

Bolded values denote significant differences.

CI, confidence interval; DMD, disease-modifying drug; MRI, magnetic resonance imaging; OR, odds ratio; scIFNβ1a, subcutaneous interferon beta-1a.

Limitations

- The ICD-9-CM code for MS does not distinguish between different MS types, such as relapsing–remitting or primary progressive MS.
- It is possible that patients were treated with DMDs prior to the 1-year pre-index (baseline) period. Additionally, patients in the sample were not necessarily newly diagnosed patients with MS.
- While adjustments were made for key differences, not all confounders may have been accounted for.
- There is a possible lack of generalizability given the inherent characteristics of claims databases and the use of an individual cohort.

Conclusions

- **In a real-world assessment of this MS population, after controlling for patient demographics and clinically meaningful measures of disease severity, treatment-naïve patients initiating scIFNβ1a had a lower likelihood of experiencing surrogates for relapse in the first year than patients initiating dimethyl fumarate or teriflunomide.**
- **Ongoing assessment of DMD treatments using real-world data is important for comparative effectiveness research.**

References

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Disclosures

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