Real-world outpatient resource use of patients with multiple sclerosis newly initiating subcutaneous interferon β-1a vs oral disease-modifying drugs

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Introduction

- As the demand for data to support decision-making escalates, there is a growing recognition that randomized controlled trials alone are not sufficient for addressing questions about the value of disease-modifying drugs (DMDs).[1]
- Payers, providers, and other stakeholders are increasingly focusing on how interventions perform in the 'real world' and what resources are consumed by the healthcare system.
- Administrative healthcare claims databases provide the ability to assess comparative effectiveness and resource use associated with the use of DMDs for multiple sclerosis (MS) in a real-world setting reflective of clinical practice in a large number of patients.[2,3]
- 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 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.[4,5]

Objective

- To utilize real-world data to evaluate healthcare resource use associated with outpatient management 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, 2014.
- 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 index 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.
- Continuous eligibility for the 12 months before and 12 months after the index date was required.

DMD treatment outcomes – outpatient resource use

- Resource use associated with outpatient management was assessed 12 months following DMD initiation and included:
  - Outpatient visits
  - Neurologist/established patient visits
  - Magnetic resonance imaging (MRI)
  - Liver function tests (LFTs) and
  - Complete blood counts (CBCs).

Descriptive/univariate analyses

- Baseline demographic and clinical characteristics were compared among the scIFNβ1a and oral DMD cohorts (ie, dimethyl fumarate, fingolimod, and teriflunomide).
- For descriptive (ie, unadjusted) analyses, categorical variables were summarized using frequencies and percentages, and 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

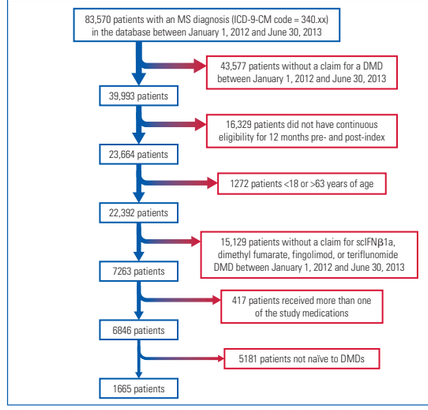
- Generalized linear models with gamma distribution and log link assessed resource use with scIFNβ1a compared with dimethyl fumarate, fingolimod, or teriflunomide.
- Covariates included patient demographics (ie, age, sex, region) and clinically meaningful measures of disease severity (ie, 90-day pre-index indicators for relapse, neurologist/established patient visits, and 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.

Results

Patient selection

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

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.

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 the oral agents; arthritis or thyroid disease compared with patients initiating teriflunomide; and anxiety compared with patients initiating dimethyl fumarate.
- 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.

Outpatient resource use – visits

- Overall outpatient and neurologist/established patient visits for the treatment cohorts during the first year on treatment are presented in **Table 3**.

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).

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).

Table 3. Unadjusted rates of post–index outpatient visits among treatment groups.

Outpatient visit	scIFNβ1a	Dimethyl fumarate	Fingolimod	Teriflunomide
n	686	406	455	118
Any outpatient visits				
Patients with visit, n (%)	682 (99.4)	403 (99.3)	455 (100.0)	118 (100.0)
No. of outpatient visits, mean (SD)	**17.6 (15.2)****	**22.4 (17.6)****	**20.6 (17.4)****	**23.9 (17.6)****
MS-related outpatient visits				
Patients with visit, n (%)	657 (95.8)	396 (97.5)	**447 (98.2)***	116 (98.3)
No. of outpatient visits, mean (SD)	6.9 (6.7)	**9.1 (9.4)****	7.3 (6.5)	8.1 (6.1)
Neurologist/established patient outpatient visits				
Patients with visit, n (%)	650 (94.8)	390 (96.1)	438 (96.3)	**117 (99.2)***
No. of outpatient visits, mean (SD)	5.5 (4.1)	**6.6 (5.1)****	**6.5 (4.8)****	**6.7 (4.7)***

Bolded values denote significant differences.
scIFNβ1a, subcutaneous interferon beta-1a; SD, standard deviation.
*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).

- The mean (standard deviation [SD]) number of 'any' outpatient visits per patient with an outpatient visit was significantly lower for scIFNβ1a (17.6 [15.2]) compared with dimethyl fumarate (22.4 [17.6]; p<0.0001), fingolimod (20.6 [17.4]; p=0.0022), and teriflunomide (23.9 [17.6]; p<0.0001).
- A significantly greater proportion of fingolimod patients (98.2%) had an MS-related outpatient visit within 1 year after initiation compared with scIFNβ1a (95.8%; p=0.0212).
- The mean (SD) number of MS-related outpatient visits per patient with an MS-related outpatient visit was significantly higher with dimethyl fumarate (9.1 [9.4]) compared with scIFNβ1a patients (6.9 [6.7]; p<0.0001).
- A significantly greater proportion of teriflunomide patients (99.2%) had a neurologist/established patient visit 1 year after initiation compared with scIFNβ1a patients (94.8%; p=0.0312).
- The mean (SD) number of neurologist/established patient visits per patient with a neurologist/established patient visit was significantly lower for scIFNβ1a (5.5 [4.1]) than for dimethyl fumarate (6.6 [5.1]; p=0.0004), fingolimod (6.5 [4.8]; p=0.0008), and teriflunomide (6.7 [4.7]; p=0.0079).

Outpatient resource use – diagnostic and laboratory tests

- Diagnostic and laboratory test use for the treatment cohorts are presented in **Table 4**.

Table 4. Unadjusted rates of post-index diagnostic and laboratory test use among treatment groups.

Diagnostic/laboratory test	scIFNβ1a	Dimethyl fumarate	Fingolimod	Teriflunomide
n	686	406	455	118
MRIs				
Patients with MRI, n (%)	328 (47.8)	**231 (56.9%)****	**270 (59.3%)****	52 (44.1)
No. of MRIs, mean (SD)	1.17 (0.46)	**1.29 (0.54)****	1.17 (0.55)	1.15 (0.41)
LFTs				
Patients with LFT, n (%)	226 (32.9)	**109 (26.8)***	141 (31.0)	49 (41.5)
No. of LFTs, mean (SD)	2.07 (1.85)	**1.66 (1.16)***	2.03 (1.20)	**2.84 (2.38)***
CBCs				
Patients with CBC, n (%)	441 (64.3)	**299 (73.6)****	299 (65.7)	73 (61.9)
No. of CBCs, mean (SD)	2.39 (2.47)	2.36 (1.68)	2.44 (1.59)	**2.97 (2.17)***

Bolded values denote significant differences.
CBC, complete blood count; LFT, liver function test; MRI, magnetic resonance imaging; scIFNβ1a, subcutaneous interferon beta-1a; SD, standard deviation.
*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).

- A significantly greater proportion of dimethyl fumarate (56.9%; p=0.0037) and fingolimod (59.3%; p=0.0001) patients had MRIs compared with scIFNβ1a patients (47.8%).
- The mean (SD) number of MRIs per patient among patients with an MRI was significantly lower for scIFNβ1a patients (1.17 [0.46]) compared with dimethyl fumarate patients (1.29 [0.54]; p=0.0046).
- A significantly lower proportion of dimethyl fumarate patients (26.8%) had an LFT compared with scIFNβ1a patients (32.9%; p=0.0347).
- The mean (SD) number of LFTs per patient among patients with an LFT was significantly lower for dimethyl fumarate patients (1.66 [1.16]; p=0.0334) and significantly higher for teriflunomide patients (2.84 [2.38]; p=0.029) compared with scIFNβ1a patients (2.07 [1.85]).
- A significantly lower proportion of scIFNβ1a patients (64.3%) had a CBC test compared with patients on dimethyl fumarate (73.6%; p=0.0014).
- The mean (SD) number of CBCs per patient with a CBC was significantly lower for scIFNβ1a patients (2.39 [2.47]) compared with teriflunomide patients (2.97 [2.17]; p=0.0247).

Multivariable analyses

- Generalized linear models predicting healthcare resource use associated with outpatient management are shown in **Table 5**.

Table 5. Generalized linear models predicting healthcare resource use associated with outpatient management.[a]

Outpatient healthcare resource	scIFNβ1a	Dimethyl fumarate	Fingolimod	Teriflunomide
Any outpatient visits				
LS mean (95% CI)	18.2 (17.0–19.4)	**21.5 (19.9–23.2)**	**21.1 (19.5–22.7)**	**22.9 (19.9–26.3)**
p value vs scIFNβ1a		**0.0005**	**0.0016**	**0.0026**
MS-related outpatient visits				
LS mean (95% CI)	6.6 (6.1–7.2)	**8.7 (7.9–9.6)**	7.5 (6.8–8.2)	7.8 (6.6–9.3)
p value vs scIFNβ1a		**<0.0001**	0.0504	0.0897
Neurologist/established patient outpatient visits				
LS mean (95% CI)	5.3 (4.9–5.7)	5.9 (5.3–6.5)	**6.2 (5.6–6.8)**	6.2 (5.2–7.5)
p value vs scIFNβ1a		0.0837	**0.0099**	0.0891
MRIs				
LS mean (95% CI)	0.54 (0.46–0.64)	**0.77 (0.63–0.94)**	**0.72 (0.60–0.88)**	0.54 (0.37–0.77)
p value vs scIFNβ1a		**0.0065**	**0.0172**	0.9612
LFTs				
LS mean (95% CI)	0.63 (0.51–0.76)	**0.45 (0.36–0.58)**	0.64 (0.51–0.82)	**1.16 (0.75–1.78)**
p value vs scIFNβ1a		**0.0364**	0.8567	**0.0091**
CBCs				
LS mean (95% CI)	1.4 (1.2–1.7)	1.7 (1.4–2.0)	1.5 (1.3–1.8)	1.7 (1.2–2.5)
p value vs scIFNβ1a		0.2185	0.5923	0.3095

Bolded values denote significance.
CBC, complete blood count; CI, confidence interval; LFT, liver function test; LS, least squares; MRI, magnetic resonance imaging; MS, multiple sclerosis; scIFNβ1a, subcutaneous interferon beta-1a.
[a]A generalized linear model with a gamma distribution and log link controlling for 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 MRI) was used for this analysis. LS means are reported.

- The least squares mean number of outpatient visits was significantly lower for scIFNβ1a (18.2) compared with dimethyl fumarate (21.5; p=0.0005), fingolimod (21.1; p=0.0016), and teriflunomide (22.9; p=0.0026).
- scIFNβ1a patients had significantly fewer MS-related outpatient visits compared with dimethyl fumarate (6.6 vs 8.7; p<0.0001), fewer neurologist/established patient visits compared with fingolimod (5.3 vs 6.2; p=0.0099), and significantly fewer MRIs compared with dimethyl fumarate (0.54 vs 0.77; p=0.0065) and fingolimod (0.54 vs 0.72; p=0.0172).
- Patients treated with scIFNβ1a had significantly fewer mean LFTs over the year than patients treated with teriflunomide (0.63 vs 1.16; p=0.0091), but significantly more LFTs over the year than dimethyl fumarate (0.63 vs 0.45; p=0.0364).
- There were no significant differences in CBCs among the DMDs.

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 baseline period. Additionally, patients in the sample may not have necessarily been 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 this real-world assessment, after adjustment for demographics and clinically meaningful disease severity indicators, several healthcare resource use measures associated with outpatient management of MS during the first year on treatment were significantly reduced in treatment-naïve patients initiating scIFNβ1a compared with patients initiating oral DMDs.**
- **The results of this study demonstrate the clinical and economic impact of scIFNβ1a versus dimethyl fumarate, fingolimod, and teriflunomide.**
- **Ongoing assessment of DMD treatments using real-world data is important for comparative effectiveness research.**

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Disclosures

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