PND89

PERSISTENCE TO ORAL AND INJECTABLE MULTIPLE SCLEROSIS DISEASE-MODIFYING THERAPIES

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Introduction

Multiple sclerosis is a chronic autoimmune disease that damages the central nervous system, with a diverse range of clinical symptoms and manifestation that is either episodic (relapsing-remitting) or progressive (primary or secondary). Prior research in Multiple Sclerosis has shown strong persistence to oral Disease-Modifying Therapies (DMT's) compared with injectables, with medication possession ratios >85%.[1] Given the increasing availability of oral DMT options, this study explores changes in real-world DMT adherence and persistence over time, across oral and injectable therapies. This study also explores differences in adherence and persistence for patients with progressive disease.

Methods

Data Sources
- This retrospective cohort study was conducted in a US medical and pharmacy claims source from the HealthVerity® Marketplace platform of data suppliers from 1/1/2013 – 12/31/2018

Data Transformation and Analysis
- Data was transformed into the OMOP Common Data Model, version 5
- Analyses were conducted using the SHYFT Quantum V6.7.0 solution

Inclusion criteria
- Patients with ≥1 MS diagnosis (ICD 9-CM 340 or ICD-10 G35) with ≥1 claims of oral, injectable, or infusion DMT during the observation period
- **Index date: first DMT Rx or procedure code within the observation period**
- Age ≥18 at index
- ≥12-month pre- and post-index continuous enrollment
- Exclusion Criteria:
  - DMT oral or injectable exposure 12-months prior to index date

Patients' persistence was assessed for:
- Oral DMT's
  - Fingolimod
  - Dimethyl fumarate
  - Dextromethorphan/Quinidine
  - Teriflunomide
  - Dalfampridine
- Injectable DMT's
  - Glatiramer acetate (Copaxone)
  - Interferon beta-1a (e.g., Rebif, Avonex)
- Adapting a previously published algorithm, sub-group assessments were conducted in patients with progressive MS[2]
  - Defined as treatment with mitoxantrone, cyclophosphamide, or methotrexate, or evidence of supportive care (home health, long term care, rehab/durable medical equipment)
- Adherence was assessed by Medication Possession Ratio (mean, median)
  - Assessed for 1st and 2nd line therapy (defined as change in therapy or gap >60 days)
- Persistence was assessed by examining discontinuation rates:
  - Time-to-discontinuation (mean, median) for 1st and 2nd line therapy
  - Kaplan-Meier curve for time to first-line treatment discontinuation
  - Cox-Proportional Hazard assessment of risk of first line treatment discontinuation
    - Covariates included: age at index, gender, history of injectable DMT use, MS relapse during baseline period (adapted from Johnson KM et al), CCI score (unadjusted for age), presence of progressive MS
- To assess changes in persistence over time, results were also assessed for January 2013- December 2015 and from January 2016-December 2018

Figure 1: Insurance Claims Dataset Attrition

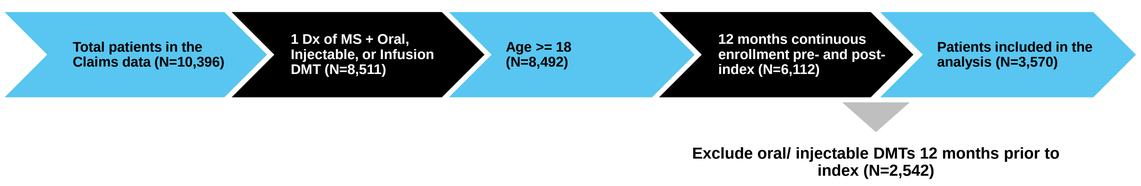
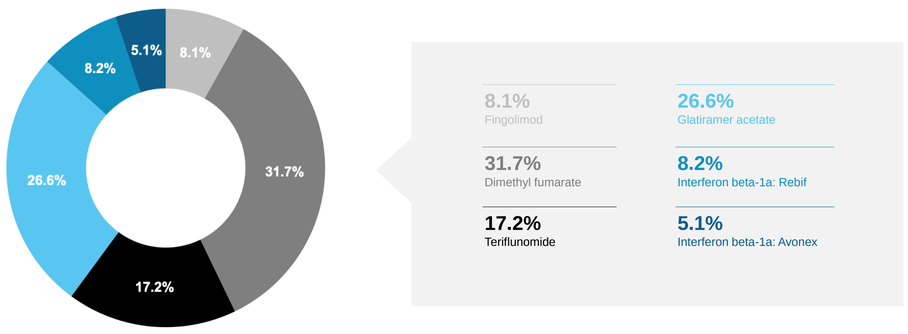


Table 1: Demographics

			Index Drug						
		Overall	Fingolimod	Dimethyl fumarate	Teriflunomide	Glatiramer acetate	Interferon beta-1a: Rebif	Interferon beta-1a: Avonex	Interferon beta-1b: Betaseron
Age At Index	Mean (SD)	48.69 (11.65)	–	–	–	–	–	–	–
	Median	49	–	–	–	–	–	–	–
Gender	FEMALE, N(%)	2,751.00 (77%)	157.00 (77%)	669.00 (76%)	351.00 (81%)	519.00 (77%)	159.00 (76%)	98.00 (76%)	–
	MALE, N(%)	797.00 (22%)	47.00 (23%)	200.00 (23%)	83.00 (19%)	146.00 (23%)	49.00 (24%)	31.00 (24%)	–
	Unknown, N (%)	22.00 (1%)	1.00 (0%)	7.00 (1%)	1.00 (0%)	5.00 (0%)	0.00 (0%)	0.00 (0%)	–
Hx of Injectable DMT 12-months before index	N (%)	1,366.00 (38%)	64 (31%)	256 (29%)	96 (22%)	657 (98%)	198 (30%)	95 (14%)	–
All-cause Hospitalization 12-months before index	N (%)	418.00 (12%)	22 (11%)	112 (13%)	58 (13%)	83 (12%)	28 (4%)	17 (3%)	–
All-cause ER 12-months before index	N (%)	176.00 (5%)	10 (5%)	40 (5%)	33 (8%)	36 (5%)	14 (2%)	3 (0%)	–
All-cause Office Visit 12-months before index	N (%)	3,459.00 (97%)	196 (96%)	841 (96%)	416 (96%)	649 (97%)	196 (29%)	123 (18%)	–
Hx of MS Relapse (12 mos. prior to index)	N (%)	552.00 (15%)	34 (17%)	140 (16%)	70 (16%)	114 (17%)	23 (3%)	22 (3%)	–
MS-related Hospitalization 12-months before index	N (%)	133.00 (4%)	11 (05%)	38 (4%)	15 (3%)	28 (4%)	4 (1%)	5 (1%)	–
MS-related ER visit 12-months before index	N (%)	15.00 (0%)	1 (0%)	5 (1%)	2 (0%)	3 (0%)	1 (0%)	0 (0%)	–
MS-related Outpatient visit 12-months before index	N (%)	2,764.00 (77%)	147 (72%)	623 (71%)	301 (69%)	462 (69%)	140 (21%)	93 (14%)	–
Count of MS Relapse	Mean (SD)	1.33 (5.73)	–	–	–	–	–	–	–
	Median	0	–	–	–	–	–	–	–
Progressive MS Patients	N (%)	89.00 (2%)	5.00 (0%)	24.00 (1%)	10.00 (0%)	21.00 (1%)	5.00 (0%)	4.00 (0%)	–
CCI Score per patient	Mean (SD)	0.33 (0.76)	–	–	–	–	–	–	–
	Median	0	–	–	–	–	–	–	–

Figure 1a: Distribution of Study Drugs at Index



Results

Overall persistence rates, as assessed by MPR, were high, in excess of 90%, regardless of oral versus injectable route of administration (**Table 2**). Time to discontinuation for was similarly high, with first-line mean days of therapy ranging from 279-465 for oral DMT's, and 329-391 days for injectables (**Table 3**). Second-line days were lower, but comparable between oral and injectables, at 122-293 and 205-213 days respectively (**Table 3**). When assessed over time, there was no significant change in mean or median MPR (data not shown).

With Oral DMT's Cox-Proportional Hazards assessment of discontinuation risk was not significant for factors assessed, although a trend towards impact of increased age and of increased CCI in non-progressive MS patients (data not shown). For Fingolimod patients, history of relapse was associated with twice the likelihood (not statistically significant) of discontinuation in progressive versus non-progressive patients.

Although sample size was limited, unadjusted persistence in patients with progressive disease did not differ significantly from non-progressives (**Table 4**). In Kaplan-Meier assessment, progressive disease was directionally associated with greater discontinuation in injectable treatments but was not statistically significant (**Figure 2**).

Table 2: Medication Possession Ratios by Line of Therapy

Medication Possession Ratio (MPR) for Oral DMT by Line of Therapy

	Fingolimod	Dimethyl fumarate	Teriflunomide	Dextromethorphan/ Quinidine	Dalfampridine
Mean	0.956	0.949	0.949	0.940	0.953
Median	0.982	0.977	0.980	1.000	0.989

	Fingolimod — 2nd line	Dimethyl fumarate — 2nd line	Teriflunomide — 2nd line	Dextromethorphan/ Quinidine — 2nd line	Dalfampridine — 2nd line
Mean	0.937	0.934	0.932	0.996	0.951
Median	0.984	0.965	0.966	1.000	1.000

Medication Possession Ratio (MPR) for Injectable DMT by Line of Therapy

	Glatiramer acetate (Copaxone)	Interferon beta-1a (Rebif)	Interferon beta-1a (Avonex)
Mean	0.956	0.940	0.953
Median	0.982	1.000	0.989

	Glatiramer acetate (Copaxone) — 2nd line	Interferon beta-1a (Rebif) — 2nd line	Interferon beta-1a (Avonex) — 2nd line
Mean	0.937	0.996	0.951
Median	0.984	1.000	1.000

Table 3: Time-to-Discontinuation by Line of Therapy

Time to Discontinuation for Oral DMT by Line of Therapy

	Fingolimod	Dimethyl fumarate	Teriflunomide	Dextromethorphan/ Quinidine	Dalfampridine
Mean	465.2	424.5	385.8	279.2	399.2
Median	362.0	328.0	270.5	171.0	244.0

	Fingolimod — 2nd line	Dimethyl fumarate — 2nd line	Teriflunomide — 2nd line	Dextromethorphan/ Quinidine — 2nd line	Dalfampridine — 2nd line
Mean	293.0	287.2	279.0	122.4	244.3
Median	195.5	196.5	195.0	121.0	158.0

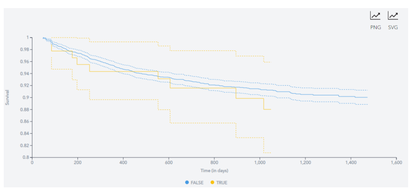
Time to Discontinuation for Injectable DMT by Line of Therapy

	Glatiramer acetate (Copaxone)	Interferon beta-1a (Rebif)	Interferon beta-1a (Avonex)
Mean	365.7	391.3	329.2
Median	257.0	267.0	260.0

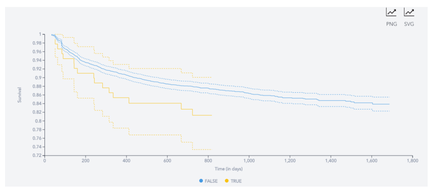
	Glatiramer acetate (Copaxone) — 2nd line	Interferon beta-1a (Rebif) — 2nd line	Interferon beta-1a (Avonex) — 2nd line
Mean	213.3	205.2	–
Median	115.0	126.0	–

Figure 2: Kaplan-Meier Curves of Time-to-Discontinuation — First Line Therapy

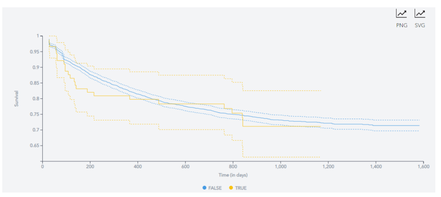
Time-to-Discontinuation of Fingolimod — First Line Therapy (by Progressive MS Status)



Time-to-Discontinuation of Teriflunomide — First Line Therapy (by Progressive MS Status)



Time-to-Discontinuation of Glatiramer acetate (Copaxone) — First Line Therapy (by Progressive MS Status)



Time-to-Discontinuation of Interferon beta-1a (Rebif) — First Line Therapy (by Progressive MS Status)

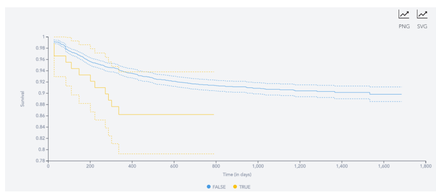


Table 4: Time-to-Discontinuation by Progressive MS Status

Time-to-Discontinuation for First-line Oral DMTs by Line of Therapy

Mean MPR	Fingolimod	Dimethyl fumarate	Teriflunomide	Dextromethorphan/ Quinidine	Dalfampridine
Progressive MS	465.2	424.5	385.8	279.2	399.2
Non-progressive MS	362.0	328.0	270.5	171.0	244.0

Mean MPR	Fingolimod — 2nd line	Dimethyl fumarate — 2nd line	Teriflunomide — 2nd line	Dextromethorphan/ Quinidine — 2nd line	Dalfampridine — 2nd line
Progressive MS	293.0	287.2	279.0	122.4	244.3
Non-progressive MS	195.5	196.5	195.0	121.0	158.0

Time-to-Discontinuation Injectable DMTs by Line of Therapy

Mean MPR	Glatiramer acetate (Copaxone)	Interferon beta-1a (Rebif)	Interferon beta-1a (Avonex)
Progressive MS	0.974	0.942	0.947
Non-progressive MS	0.956	0.950	0.963

Mean MPR	Glatiramer acetate (Copaxone) — 2nd line	Interferon beta-1a (Rebif) — 2nd line	Interferon beta-1a (Avonex) — 2nd line
Progressive MS	1.0	0.983	0.969
Non-progressive MS	1.0	0.989	1.0

Conclusions

Oral DMT's continue to demonstrate high levels of persistence and increasing use in real world settings. Possible next steps include further exploration of use by Relapsing-Remitting versus Chronic Progressive Multiple Sclerosis, particularly in data sources with linkages to functional impact or the ability to examine frequency and severity of relapse episodes. Given documented patterns of primary non-adherence in other chronic autoimmune conditions, future analysis could also explore fill patterns in linked EMR-claims datasets.[3]

References

1. Johnson KM et al. Real-world adherence and persistence to oral disease-modifying therapies in Multiple Sclerosis over 1 year. JMCP August 2017, 23(8): 844-852.
2. Le HV et al. Identifying patients with relapsing-remitting multiple sclerosis using algorithms applied to US integrated delivery network health care data. Value in Health June14, 2018
3. Harnett J et al. Primary nonadherence, associated clinical outcomes, and health care resource use among patients with rheumatoid arthritis prescribed treatment with injectable biologic disease-modifying antirheumatic drugs. J Manag Care Spec Pharm. 2016 Mar;22(3):209-18