Exploring Demographic, Geographical, and Clinical Factors Associated with Persistence to High-Efficacy Therapies in Multiple Sclerosis

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Abstract

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Background: High-efficacy disease-modifying therapies (DMTs) in multiple sclerosis (MS) are defined as those that reduce relapses by 50%. A majority of these high-efficacy DMTs are administered intravenously at varying intervals, including alemtuzumab every 365 days, mitoxantrone every 90 days, natalizumab every 28 days, ocrelizumab every 182 days, and ublituximab every 168 days. While several studies have investigated the rates of persistence on these high-efficacy DMTs, no studies to date have investigated patient factors associated with the persistence of these high-efficacy infusion DMTs.

Objective: To identify demographic, geographical, and clinical factors associated with the persistence of high-efficacy infusion DMTs in MS after 12 months from initiation.

Methods: We conducted a retrospective cohort study using the Merative™ Marketscan® Commercial Database. We identified patients diagnosed with MS starting high-efficacy infusion DMTs between January 1, 2018, and December 31, 2020. Persistence was defined as having no evidence of switching to a new therapy or having no gap greater than 60 days beyond the recommended dosing regimens. For each DMT, we used an adjusted multivariable logistic regression model to assess the association between the binary outcome of persistence for 12 months and age, sex, level of rurality, region, health plan type, employment classification,

Charlson Comorbidity Index score, mental health comorbidity status, length of MS diagnosis, and presence of a recent MS relapse event. We ran additional scenario analyses to compare the probability of persistence using varying persistence definitions found in the literature.

Results: We found that a higher proportion of patients were persistent at 12 months on ocrelizumab (80.9%) versus natalizumab (66.3%). Among patients who survived and were persistent for 12 months, a higher proportion of patients were persistent at 24 months on natalizumab (57.5%) versus alemtuzumab (39.8%) or ocrelizumab (49.8%). Age, sex, region, health plan type, employment classification, mental health comorbidity status, and presence of a recent MS relapse event were not significantly associated with persistence to natalizumab or ocrelizumab at 12 months. We found that the odds of persistence on ocrelizumab were significantly higher in patients living in rural areas versus those living in urban areas (OR: 0.73, 95% CI: 0.54-0.98, p-value: 0.039) and in patients who had been recently diagnosed with MS before starting an infusion DMT (OR: 1.39, 95% CI: 1.05-1.83, p-value: 0.020). The odds of persistence on natalizumab were significantly higher in patients with fewer than two comorbidities (OR: 0.58, 95% CI: 0.35-0.96, p-value: 0.041) and in patients who had been recently diagnosed with MS before starting an infusion DMT (OR: 2.24, 95% CI: 1.68-2.98, p-value<0.001).

Conclusion: At 12 months post-index, ocrelizumab was found to have a higher probability of persistence compared to natalizumab, which may be explained by its extended dosing regimen of 182 days versus 28 days. In patients taking ocrelizumab, higher persistence was significantly associated with those living in rural areas compared to urban areas and those who had been recently diagnosed with MS before starting an infusion DMT. In patients on natalizumab, higher persistence was significantly associated with those with fewer than two comorbidities and patients who had been diagnosed with MS within six months before DMT initiation. Future research could explore persistence trends among newer high-efficacy DMTs, including ofatumumab and ublituximab.

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INTRODUCTION

Multiple Sclerosis (MS) is an autoimmune-mediated neurological disorder that causes central nervous system damage leading to neurological deficits.[1,2] One million individuals in the United States are living with MS; a majority are females between 20-50 years old at diagnosis.[3] Due to the young age at onset and the progressive neurological complications, MS leads to significant social and economic losses in the young working population.[1,2] While there is no cure for MS, disease-modifying therapies (DMTs) reduce the activity and progression of MS. High-efficacy DMTs are defined as interventions that reduce relapses by 50% and include alemtuzumab (Lemtrada), cladribine (Mavenclad), mitoxantrone (Novantrone), natalizumab (Tysabri), ocrelizumab (Ocrevus), ofatumumab (Kesimpta), and ublituximab (Briumvi).[4] A majority of these high-efficacy DMTs are administered intravenously and at varying intervals, including alemtuzumab every 365 days, mitoxantrone every 90 days, natalizumab every 28 days, ocrelizumab every 182 days, and ublituximab every 168 days.

Persistence in these high-efficacy DMTs is important for patient outcomes, such as preventing MS progression and relapse. Persistence is defined as the continuation of medication from the time of initiation without any changes in therapy or significant gaps in coverage, such as no gaps greater than 60 days beyond the recommended time between infusions.[5] However, non-persistence may occur for a variety of reasons including lack of efficacy, medication intolerance, limited access to therapy, patient preference, or safety reasons.[5] Literature has shown that between 19-28% of patients discontinue or switch therapy at least once within the first two years of initiating a DMT.[6,7] Given this, the first two years are an important timeline to identify which patients are most likely to be non-persistent. No studies to date have investigated patient factors associated with the persistence of these high-efficacy infusion DMTs.[5] An improved understanding of the factors associated with persistence to high-efficacy infusion DMTs could aid in developing strategies to improve persistence.

OBJECTIVE

The objective of this study was to describe the proportion of patients persistent to high-efficacy infusion DMTs at 12 and 24 months after initiating therapy as well as to identify demographic,

geographical, and clinical factors associated with the persistence to high-efficacy infusion DMTs in patients with MS evaluated during the first 12 months of new initiation.

METHODS

Study Design and Data Source

We conducted a retrospective cohort study utilizing medical and pharmacy claims from the Merative™ Marketscan® Commercial Database, which includes individual-level, deidentified health data on more than 264 million individuals.[8] This database includes prescription, inpatient, and outpatient service utilization information.

DMT Selection

High-efficacy infusion DMTs were identified through their corresponding Healthcare Common Procedure Coding System (HCPCS) codes, including alemtuzumab (HCPCS: *J0202)*, mitoxantrone (HCPCS: J9293), natalizumab (HCPCS: *J9293)*, ocrelizumab (HCPCS: *J2350),* and ublituximab (HCPCS: *J3590*). Of the possible high-efficacy infusion DMTs, we excluded mitoxantrone due to an insufficient sample size during the study period and ublituximab, introduced to the market in 2022, due to a lack of available data.

According to the labels, the dosing schedules used for each of the DMTs analyzed in this study included every 365 days for alemtuzumab, 28 days for natalizumab, and 182 days for ocrelizumab. Three cohorts were constructed for each of the high-efficacy DMTs (alemtuzumab, natalizumab, and ocrelizumab) included in the analysis given the variation in dosing frequency.

Study Period

As shown in Figure 1, the study period spanned from November 1, 2016, to December 31, 2022. The study period start date was selected to ensure the three included DMTs, alemtuzumab, natalizumab, and ocrelizumab, were available with permanent HCPCS codes during the index period. Ocrelizumab received a permanent HCPCS code at the end of 2017. A 14-month wash-out period was implemented to ensure all participants were new starts to the infusion DMTs. The 14 months accounted for the longest infusion interval allowed in the persistence definition, 365 days for alemtuzumab infusions plus the possible 60-day gap, to ensure all patients were new

starts. December 31, 2022 was the end of available data and was used as the study period endpoint. The index period was from January 1, 2018 to December 31, 2020. It was used to identify new DMT starts and allowed for a minimum of two years of follow-up. The index date was the first infusion claim for alemtuzumab, natalizumab, or ocrelizumab.

Participant Selection

For this study, participants were required to be adults (≥ 18 years old) with an MS diagnosis. MS diagnoses were identified using the International Classification of Diseases (ICD-10) code: *G35*. Patients were required to have at least two outpatient claims for MS in either of the diagnosis positions. Patients were required to be new starts to a high-efficacy infusion DMT defined as having at least two outpatient claims for the same high-efficacy infusion DMT during the study period. To ensure only new starts were included, patients could not have had a claim for the same high-efficacy infusion DMT during the 14 months before the index date. Patients were also required to have 14 months of continuous enrollment before and after the index date to capture the washout period and primary outcome.

Characteristics of Interest

The following factors were assessed for association with the primary outcome of persistence at 12 months: age, sex, health plan type, employment classification, geographic region, level of rurality, Charlson Comorbidity Index (CCI) score, presence of a mental health condition, recent diagnosis of MS, and a recent MS relapse event. These factors were chosen given past literature findings of other DMT associations with persistence or adherence as well as available characteristics in Merative™ Marketscan® Commercial Database.

Demographic Characteristics

Age was analyzed as a continuous variable. Sex was analyzed as a dichotomous variable. Health plan types were grouped based on similar payment structures and offered features. These groups included consumer-driven health plan/high-deductible health plan (CDHP/HDHP), exclusive provider organization/preferred provider organization (EPO/PPO), B/MM/COMP basic/major medical/comprehensive (B/MM/COMP), health maintenance organization (HMO), and non-capitated point of service/capitated or partially capitated point of service (POS). The

employment classification of the primary beneficiary was dichotomized as either salaried or hourly employment for analysis.

Geographical Characteristics

Geographic region was analyzed using the United States regions designated in the Merative™ Marketscan® Commercial Database, including Northeast, North Central, South, or West. The level of rurality was determined using the Merative™ Marketscan® Commercial Database metropolitan statistical area (MSA) variable, which was mapped to the associated Federal Information Processing Series (FIPS) code using the National Bureau of Economic Research's (NBER) county crosswalk data. The FIPS codes were used to determine rurality classification based on the National Center for Health Statistics' (NCHS) Urban-Rural Classification Scheme for Counties.[9,10] Outpatient prescription claims with "0 – non-MSA" were classified as "rural." MSAs not listed in NBER's county crosswalk were excluded from the rurality analysis. For analysis, rurality was dichotomized into non-metropolitan (rural, non-core, or micropolitan areas) or metropolitan (small, medium, large, or central metropolitan areas) according to the Health Resources and Services Administration definitions.[11]

Clinical Characteristics

All clinical characteristics were identified in the pre-index period. The Charlson Comorbidity Index (CCI) score was analyzed as a categorical variable with either 0, 1, or ≥ 2 comorbid conditions.[12] The presence of a mental health condition was identified by looking at ICD-10 diagnosis codes, including *F01 – F99*, and was a dichotomous variable with a mental health diagnosis or not. Patients were also dichotomized based on the length of MS diagnoses as either newly diagnosed or not. Newly diagnosed patients were identified by having no outpatient or inpatient claims with a diagnosis code of MS (ICD-10: *G35*) nor any DMT prescription claims longer than six months before the index date. The final clinical characteristic was a recent MS relapse event, which was identified using a previously validated algorithm that included an inpatient claim with a primary diagnosis of MS (ICD-10: *G35*), an outpatient claim with a primary diagnosis of MS (ICD-10: *G35*) either with the receipt of an intravenous corticosteroid or corticotropin (i.e., adrenocorticotropic hormone) or preceding a prescription claim for oral high-dose corticosteroids with less than a 30-day supply.[13]

Study Outcomes

The primary endpoint was persistence during the first 12 months of starting a DMT. Persistence in this study was defined as having no gap in coverage more than 60 days beyond the recommended infusion interval and having no evidence of starting other DMT medications (Appendix 1). Given alemtuzumab's dosing schedule of one dose every 365 days, it was not included in the primary endpoint since all patients would have been considered persistent under the current definition. The secondary endpoint was persistence at 24-months post-index. This outcome was only evaluated among patients, who were considered persistent at 12 months and had survived to have continuous enrollment through 24-months post-index.

We conducted two additional scenario analyses to assess the impact of the definition of persistence. One alternative definition was the receipt of a dose at 12-months post-index plus or minus two months. The second alternative definition was having no gap in coverage more than 90 days beyond the recommended infusion interval and having no evidence of starting other DMT medications (Appendix 1).

Statistical Analysis

In the primary analysis, we used an adjusted multivariable logistic regression to assess the association between the binary outcome of persistence for 12 months and demographic, geographical, and clinical characteristics. We used an alpha level of 0.05 and calculated 95% confidence intervals.

Software

SAS version 9.4 (SAS Institute Inc., Cary, NC) was used to obtain the dataset of each of the cohorts. R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all other statistical analyses completed.

RESULTS

Baseline characteristics for each of the three high-efficacy infusion DMT cohorts are presented in Table 1. Our sample included 4,722 individuals with 231 on alemtuzumab, 1,402 on

natalizumab, and 3,089 on ocrelizumab. Across the cohorts, the mean ages were approximately 42-44 years old and predominately female (72-77%). The groups were similar in terms of other demographic and geographical characteristics. However, natalizumab had the most patients with a CCI score of 0 (82.6% versus 71.9% for alemtuzumab and 72.3% for ocrelizumab), fewer patients with a mental health comorbidity (31.1% versus 39.4% for alemtuzumab and 42.7% for ocrelizumab), and most with a recent MS diagnosis (43.3% versus 10.4% for alemtuzumab and 19.0% for ocrelizumab). Alemtuzumab had the most patients who had experienced a recent relapse event (32.5% versus 22.1% for natalizumab and 26.5% for ocrelizumab).

The proportion of patients persistent at 12 and 24 months for the three high-efficacy infusion DMT cohorts are presented in Table 2. We found that a higher proportion of patients were persistent at 12 months on ocrelizumab (80.9%) versus natalizumab (66.3%). Among patients who survived and were persistent for 12 months, a higher proportion of patients were persistent at 24 months on natalizumab (57.5%) versus alemtuzumab (39.8%) or ocrelizumab (49.8%).

Primary Analysis

Demographic Factors

The results of the multivariate logistic regression are presented in Table 3. Age and sex were not found to be significantly associated with persistence at 12 months post-initiation to either natalizumab or ocrelizumab. However, in the natalizumab cohort, males tended to be less persistent compared to females (OR: 0.76, 95% CI: 0.56-1.02, p-value: 0.16). No significant associations were found for either of the DMT cohorts with health plan types or employment classification and persistence.

Geographic Factors

No significant associations were found between geographic region and either natalizumab or ocrelizumab persistence. Ocrelizumab patients had higher odds of persistence among rural patients compared to patients living in metropolitan areas (OR: 0.73, 95% CI: 0.54-0.98, p-value: 0.039).

Clinical Factors

Natalizumab patients with at least two comorbidities, using the CCI score, compared to those with a score of 0 had lower odds of persistence (OR: 0.59, 95% CI: 0.36-0.98, p-value: 0.041). There was no significant association in either cohort between mental health comorbidities and persistence. A recent MS diagnosis was significantly associated with persistence in both the natalizumab and ocrelizumab cohorts (natalizumab - OR: 2.24, 95% CI: 1.68-2.98, p-value <0.001; ocrelizumab – OR: 1.39, 95% CI: 1 .05-1.83, p-value: 0.020). A recent relapse event was not found to be significantly associated with the odds of persistence in either cohort.

Scenario Analyses

Scenario analysis results are available in Supplementary Material Table 1. In the first scenario analysis using a persistence definition of receiving a dose at 12 ± 2 months, the proportion of patients, who were persistent on natalizumab and ocrelizumab, was 71.4% and 63.1%, respectively. Then, in the second scenario analysis using the persistence definition allowing for no greater than a 90-day gap beyond the recommended dosing regimen and no evidence of new DMT therapy, the proportion of patients persistent to natalizumab and ocrelizumab was 71.2% and 82.0%, respectively, at 12 months post-index date.

DISCUSSION

In this analysis, ocrelizumab had higher persistence at 12-months compared to natalizumab, 80.9% compared to 66.3%, which is likely explained by the dosing frequency of ocrelizumab (given every 182 days) compared to natalizumab (given every 28 days). Our findings align with results from several retrospective claims studies that found ocrelizumab to have higher rates of persistence compared to natalizumab.[1,14] However, at the 24-month mark, natalizumab had the highest persistence at 57.5% compared to 39.8% with alemtuzumab and 49.8% with ocrelizumab. This was contrary to another claims study that found ocrelizumab to have an 80% persistence rate at 24 months and natalizumab to have a 54% persistence rate.[14] These differences may be related to their smaller sample size for both DMTs.[14] Additionally, we found that using alternative definitions for persistence in the scenario analyses, such as allowing for 90 days

beyond the recommended dosing regimen instead of 60 days, did not significantly change the results or conclusions.

We examined the associations between demographic, geographic, and clinical characteristics with persistence to high-efficacy infusion DMTs in MS patients. We did not find any associations with persistence at 12 months post-DMT initiation and sex, age, health plan type, employment classification, geographic region, mental health comorbidity, or recent MS relapse events in either the natalizumab or ocrelizumab cohorts.

Rurality was found to be significantly associated with persistence in the ocrelizumab group; those living in rural areas had higher odds of persistence compared to patients living in metropolitan areas (OR: 0.73, 95% CI: 0.54-0.98, p-value <0.05). The extended dosing interval of ocrelizumab (182 days between infusions) may explain this finding as it allows for fewer trips to the pharmacy or outpatient clinics, which may be preferable for those living farther from healthcare resources. We did not find any literature on the impact of rurality specifically on persistence to infusion therapies in MS. However, one study looking at adherence to infusion therapies in patients with rheumatoid arthritis found that living in rural areas was associated with better adherence.[15] One study found no difference in urban versus rural classifications with associations to persistence; however, they were investigating only intramuscular and subcutaneous injections, which do not offer extended interval dosing like infusion therapies and are often administered at home by the patients.[16] It would be beneficial for future studies to continue to investigate this association with rurality and persistence to infusion therapies with extended dosing regimens.

We found that a Charlson Comorbidity Index score of greater than two was significantly associated with natalizumab persistence at 12 months (OR: 0.58, 95% CI: 0.35-0.96, p-value: 0.041*). This trend could be explained by patients facing challenges in managing multiple disease states concurrently. This aligns with a prior retrospective cohort study that found comorbid conditions in MS were associated with lower persistence to treatment with a hazard ratio of 1.42.[17] In this study, patients with more comorbid conditions were most likely to discontinue DMT therapy due to intolerances.[17] In our study, we specifically investigated if

mental health comorbidities had an impact on persistence to infusion DMTs given that approximately 23.7% and 21.9% of MS patients have a diagnosis of depression and anxiety respectively; we did not find a significant association with mental health comorbidities and persistence.[18] Future work could further investigate which comorbid conditions were most associated with non-persistence to therapy to better identify these at-risk patients.

A new MS diagnosis within 6 months of starting an infusion DMT was significantly associated with persistence for both natalizumab and ocrelizumab (natalizumab – OR: 2.24, 95% CI: 1.68-2.98, p-value<0.001; ocrelizumab – OR: 1.39, 95% CI: 1.05-1.83, p-value 0.020). One possible explanation for these results is that those with newer MS diagnoses may not have as severe disease as those who have had longer MS diagnoses. Those who have had MS for longer may need to instead switch DMTs to find an optimal therapy. One large observational, multicenter, multinational study (n=2,648) similarly found that patients adherent to injectable DMTs had significantly shorter durations of disease.[19]

Given the use of claims data, we had limited clinical information available that may be important in the persistence to these therapies, including the type of MS patients have, identification of MS relapse events rather than estimating these events through an algorithm that had a positive predictive value of 67.3%, length of a patient's MS diagnosis instead of an estimation, and reasons for therapy discontinuation or switches. Another limitation was that we applied the generic labeled dosing schedules for the persistence definitions, but this may not reflect prescribing patterns used in the real world for these therapies. Additionally, requiring 14 months of pre- and post-index continuous enrollment for gathering characteristics and for follow-up may have led to selection bias; the sicker patients, who may have died during the follow-up period, may have been excluded from the study due to the required enrollment criteria. Also, multiple comparisons were made in the multivariable logistic regression model; significant results may have been due to chance.

CONCLUSION

We analyzed the association between demographic, geographic, and clinical characteristics with persistence to high-efficacy infusion DMTs in patients diagnosed with MS in a US commercially

insured population. We found that the probability of persistence was significantly higher in patients taking ocrelizumab living in rural areas versus urban areas, patients on natalizumab with fewer than two comorbidities compared to those with two or more comorbidities, and patients on natalizumab or ocrelizumab who had been diagnosed with MS in the six months before starting an infusion DMT compared versus longer than six months These findings highlight how such characteristics should be considered when determining a patient's risk for non-persistence. Future research could expand on this work by exploring persistence trends among other key patient characteristics, applying various persistence definitions, and among newer high-efficacy DMTs, including ofatumumab and ublituximab.

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FIGURES AND TABLES

Figure 1. Overall Study Design

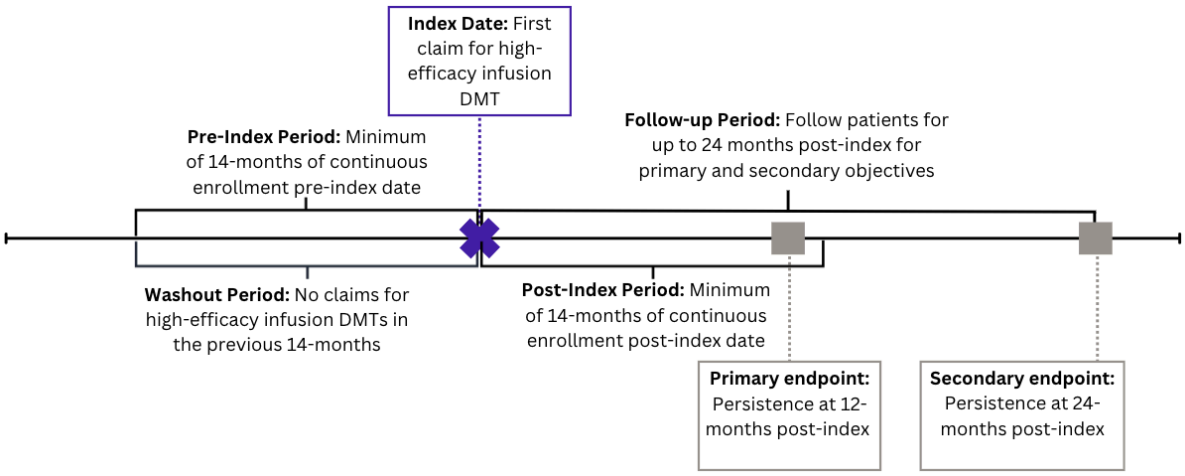

Figure 2. Cohort Attrition Diagrams

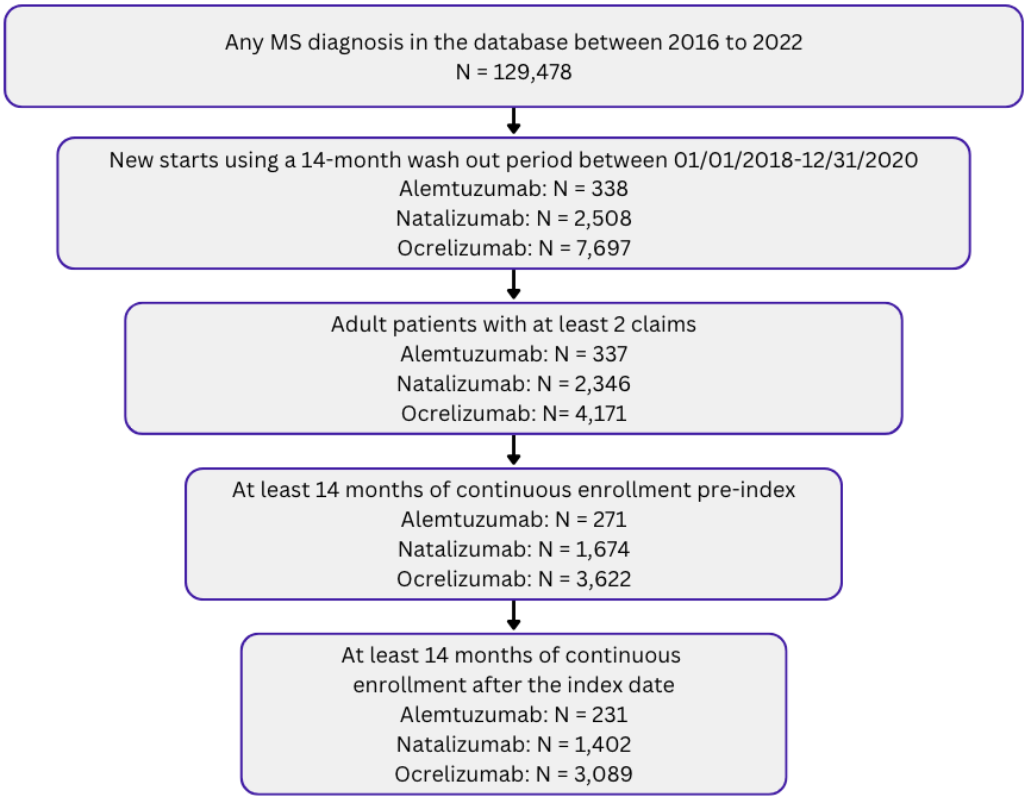

Table 1. Baseline Demographics

	Alemtuzumab	Natalizumab	Ocrelizumab
	N = 231	N = 1402	N = 3089
Age [mean (sd)]	42.9 (10.5)	42.1 (10.3)	44.6 (10.3)
<35 years [n (%)]	56 (23.9%)	359 (25.6%)	555 (18.0%)
35-44 years [n (%)]	74 (31.6%)	441 (31.5%	922 (29.8%)
45-54 years [n (%)]	66 (28.2%)	436 (31.1%)	1000 (32.4%)
≥ 55 years [n (%)]	38 (16.2%)	166 (11.8%)	612 (19.8%)
Sex (Females) [n (%)]	175 (75.8%)	1072 (76.5%)	2247 (72.7%)
Health Plan Type [n (%)]			
CDHP/HDHP	58 (25.6%)	290 (20.6%)	733 (24.3%)
EPO/PPO	117 (51.5%)	700 (51.0%)	1579 (52.4%)
B/MM/COMP	4 (1.8%)	17 (1.2%)	84 (2.8%)
HMO	23 (10.1%)	159 (11.6%)	367 (12.2%)
POS	24 (10.6%)	207 (15.1%)	253 (8.4%)
Employment Classification (Salaried) [n (%)]	62 (26.9%)	318 (22.7%)	942 (30.5%)
Geographic Region [n (%)]			
Northeast	24 (10.4%)	250 (17.8%)	595 (19.3%)
North Central	51 (22.1%)	300 (21.4%)	791 (25.6%)
South	136 (58.9%)	619 (44.2%)	1282 (41.8%)
West	19 (8.2%)	230 (16.4%)	405 (13.1%)
Level of Rurality [n (%)]			
Non-Metropolitan	31 (15.5%)	193 (16.7%)	399 (16.1%)
Metropolitan	169 (84.5%)	961 (83.3%)	2079 (83.9%)
CCI Score Categories [n (%)]			
0	166 (71.9%)	1158 (82.6%)	2233 (72.3%)
1	26 (11.3%)	138 (9.8%)	437 (14.1%)
≥2	40 (16.9%)	106 (7.6%)	419 (13.6%)
Had a Mental Health Comorbidity [n (%)]	91 (39.4%)	436 (31.1%)	1318 (42.7%)
Had a recent MS Diagnosis [n (%)]	24 (10.4%)	607 (43.3%)	587 (19.0%)
Had a recent MS Relapse Event [n (%)]	75 (32.5%)	310 (22.1%)	817 (26.5%)

Abbreviations: CDHP/HDHP: consumer-driven health plan/high deductible health plan, EPO/PPO: exclusive provider organization/preferred provider organization, B/MM/COMP: basic/major medical/comprehensive, HMO: health maintenance organization, POS: capitated and non-capitated point of service, CCI: Charlson Comorbidity Index

Table 2. Proportion of Patients Persistent at Primary and Secondary Endpoints

	Alemtuzumab	Natalizumab	Ocrelizumab
Sample Size at 12 months	231	1402	3089
Persistence at 12 months [n (%)]	- [a]	929 (66.3%)	2500 (80.9%)
Sample Size at 24 months	201	831	2254
Persistence at 24 months [n (%)]	80 (39.8%)	478 (57.5%)	1123 (49.8%)

[a]: Alemtuzumab was not included in the descriptive analysis of the proportion of patients persistent at the primary endpoint of 12 months post-initiation given its dosing schedule. Alemtuzumab is dosed every 365, which would have made all patients in this cohort be considered persistent under the applied persistent definition.

Table 3. Adjusted Odds Ratios (95% CI) of Primary Outcome

	Natalizumab	p-value	Ocrelizumab	p-value
N	1402		3089	
Age	1.01 (1.00-1.02)	0.07	1.00 (0.99-1.01)	0.58
Sex				
Female	1.00 (Ref)		1.00 (Ref)	
Male	0.76 (0.56-1.02)	0.07	1.02 (0.81-1.28)	0.87
Health Plan Type				
CDHP/HDHP	1.00 (Ref)		1.00 (Ref)	
EPO/PPO	0.89 (0.64-1.23)	0.47	0.87 (0.68-1.12)	0.28
B/MM/COMP	1.36 (0.40-4.59)	0.62	1.67 (0.73-3.80)	0.22
HMO	1.46 (0.90-2.38)	0.13	1.05 (0.72-1.52)	0.81
POS	0.72 (0.46-1.13)	0.15	0.88 (0.58-1.33)	0.56
Employment Classification				
Salary	1.00 (Ref)		1.00 (Ref)	
Hourly	1.01 (0.74-1.38)	0.94	1.09 (0.88-1.37)	0.42
Geographic Region				
Northeast	1.00 (Ref)		1.00 (Ref)	
North Central	1.12 (0.70-1.78)	0.63	0.91 (0.65-1.27)	0.58
South	0.90 (0.59-1.38)	0.63	1.00 (0.73-1.37)	0.99
West	1.00 (0.61-1.64)	0.99	0.74 (0.51-1.06)	0.10
Rurality				
Rural	1.00 (Ref)		1.00 (Ref)	
Metro	0.98 (0.69-1.38)	0.90	0.73 (0.54-0.98)	0.039*
CCI Score Categories				
0	1.00 (Ref)		1.00 (Ref)	
1	1.23 (0.78-1.93)	0.37	1.00 (0.74-1.35)	0.98
≥2	0.59 (0.36-0.98)	0.041*	1.02 (0.75-1.38)	0.93
Mental Health Comorbidity				
No Comorbidity	1.00 (Ref)		1.00 (Ref)	
Has Comorbidity	1.03 (0.77-1.37)	0.87	1.10 (0.90-1.36)	0.36
MS Diagnosis within the Year				
No Recent Diagnosis	1.00 (Ref)		1.00 (Ref)	
Recent Diagnosis	2.24 (1.68-2.98)	<0.001*	1.39 (1.05-1.83)	0.020*
MS Relapse Event within the Year				
No Relapse Event	1.00 (Ref)		1.00 (Ref)	
Recent Relapse Event	1.04 (0.76-1.44)	0.79	0.85 (0.68-1.07)	0.20

APPENDIX

Appendix 1. DMT NDC and HCPCS Codes

Generic Name	Route of administration	NDC or HCPCS Code
Alemtuzumab	IV	J0202
Cladribine	PO	63323-0140-10, 00143-9871-01, 42658-0010-01, 67457-0450-10, 42658-0010-91, 67457-0451-10, 44087-4000-09, 44087-4000-07, 44087-4000-06, 44087-4000-00, 44087-4000-05, 44087-4000-08, 44087-4000-04
Mitoxantrone	IV	J9293
Natalizumab	IV	J2323
Ocrelizumab	IV	J2350
Ofatumumab	SC	J9302, 00078-1007-68
Ublituximab	IV	J2329
Dimethyl fumarate	PO	16729-0416-04, 16729-0417-59, 16729-0417-12, 69238-1318-04, 69238-1626-08, 69238-1319-06, 69238-1626-04, 67877-0555-14, 67877-0556-60, 59651-0084-60, 59651-0083-14, 31722-0658-32, 31722-0657-31, 69097-0323-03, 69097-0322-28, 69097-0322-89, 69097-0323-88, 43598-0430-60, 43598-0429-52, 00378-0396-14, 00378-0399-18, 00378-0399-91, 51927-2929-00, 70512-0852-14, 70512-0853-60, 43547-0024-14, 43547-0025-60, 24979-0128-04, 24979-0127-21, 64406-0005-01, 64406-0006-02, 69238-1626-03, 67877-0557-39, 31722-0680-60, 69097-0552-03, 64406-0007-03
Diroximel fumarate	PO	64406-0020-03
Monomethyl fumarate	PO	69387-0001-01
Fingolimod	PO	70709-0062-30, 70709-0065-30, 16729-0342-10, 60505-4332-03, 67877-0476-30, 31722-0889-30, 43598-0285-30, 68462-0166-30, 64980-0449-03, 00480-7820-56, 68382-0912-06, 00078-0607-15, 00078-0965-89, 00078-0607-89
Ponesimod	PO	50458-0720-30, 50458-0707-14
Ozanimod	PO	59572-0820-30, 59572-0890-21, 59572-0890-30, 59572-0810-07, 59572-0890-07, 59572-0890-28
Siponimod	PO	00078-0979-50, 00078-0986-45, 00078-0986-15, 00078-1014-15, 00078-0979-89, 00078-0979-12
Glatiramer acetate	SC	J1595, 68546-0325-12, 68546-0317-30, 00378-6961-32, 00378-6960-93, 00378-6960-32, 00378-6961-12, 00781-3250-89, 00781-3234-34
Interferon beta-1a	IM, SC	J1826, 59627-0001-04, 59627-0222-05, 59627-0002-06, 59627-0333-04, 59627-0003-01, 44087-

		0044-03, 44087-0022-03, 44087-3322-01, 44087-3344-01, 44087-8822-01, 44087-0188-01
Interferon beta-1b	SC	J1830, Q3027, Q3208, 50419-0523-35, 50419-0524-01, 50419-0524-35, 50419-0523-09, 00078-0569-12, 00078-0569-61, 00078-0569-99, 50419-0523-25
Peginterferon beta-1a	SC	64406-0017-01, 64406-0011-01, 64406-0015-01, 64406-0012-01, 64406-0016-01
Teriflunomide	PO	58468-0210-04, 58468-0211-04, 16729-0399-10, 16729-0400-10, 62332-0313-30, 62332-0314-30, 69238-1304-06, 69238-1303-06, 60505-4478-03, 60505-4477-03, 59651-0055-30, 59651-0054-30, 42291-0830-30, 42291-0831-30, 70377-0017-11, 70377-0018-11, 31722-0246-30, 31722-0247-30, 43598-0281-30, 43598-0282-30, 68462-0423-30, 68462-0424-30, 00781-5755-31, 00781-5747-31, 70512-0850-28, 70512-0851-28, 00480-3157-56, 00480-3156-56, 70710-1114-03, 70710-1115-03
Daclizumab beta	SC	J7513

SUPPLEMENTAL MATERIAL

Table 1. Scenario Analysis Results

	Natalizumab	Ocrelizumab
Sample Size at 12 months	1402	3089
Primary Definition at 12 months [n (%)]	929 (66.3%)	2500 (80.9%)
Scenario Analysis Definition 1 at 12 months [n (%)]	1001 (71.4%)	1948 (63.1%)
Scenario Analysis Definition 2 at 12 months [n (%)]	998 (71.2%)	2534 (82.0%