Capstone for Impact: A Retrospective Analysis of Insurance Policy Impact on the Choice of Multiple Sclerosis Disease Modifying Therapies

Abstract:
Background: Financial barriers to disease modifying therapies (DMT) for multiple sclerosis (MS) have been widely reported; yet the impact of insurance restrictions on DMT choice and adherence has been studied to a lesser extent.

Objective: To evaluate insurance policy restrictions experienced by patients pursuing disease modifying therapies for MS.

Methods: A retrospective chart review of patients seen in the MS specialty clinic at Alfred Taubman Health Care Center of Michigan Medicine between January 1st, 2020 and February 29th, 2020 was performed. Medical records were assessed for insurance challenges experienced by patients with MS during initiation and transition between DMTs.

Results: 460 patients were evaluated in the study of which 350 (76.1%) carried a diagnosis of MS. Of these patients, 72 (20.6%) were unable to start or continue their desired DMT, as agreed upon by the provider and patient, at some point during their treatment course due to financial limitations related to their insurance coverage. The most common limitation was a required step therapy approach to treatment, followed by lost or reduced insurance coverage, and high copays among others. DMTs found to be difficult to access financially were glatiramer acetate (17.7%), dimethyl fumarate (17.7%), ocrelizumab (15.2%), beta-interferon-1a (12.7%), natalizumab (11.4%), teriflunomide (7.6%), rituximab (6.3%), fingolimod (6.3%), beta-interferon-1b (2.5%) and alemtuzumab (2.5%). Tecfidera and beta-interferon-1a were the DMTs most likely to be discontinued secondary to high copays. Ocrelizumab was the most likely DMT to be rejected by insurance due to a required step therapy approach to treatment, followed by dimethyl fumarate, natalizumab, fingolimod, alemtuzumab, and teriflunomide. Patients experienced most of these insurance difficulties at the initiation of treatment with DMTs (65.8%). Due to lack of insurance coverage, 46 (12.1%) patients were off DMT at some point during their MS course.

Conclusions: One in five patients with MS were found to experience difficulty accessing DMTs secondary to insurance restrictions, of which 63.9% were off DMT completely at some point during their MS course. Step therapy as a required approach to treatment was the most common barrier to desired DMT treatment. Financial barriers to DMT use secondary to insurance restrictions experienced by patients with MS should be further elucidated and alleviated by both insurance and drug companies.

Introduction:
The treatment of multiple sclerosis (MS) has evolved rapidly since the approval of interferon beta yet access to disease modifying therapy (DMT) remains a significant challenge[1, 2]. Financial limitations and insurance restrictions are frequently cited barriers to both starting and

transitioning between DMTs[3]. These factors influence the approach to selecting a DMT by both patients and providers[4].

The choice of DMT for MS treatment is influenced by Individual patient and drug-specific factors[5]. Perceived severity of MS course, patient views and preferences about drug tolerably, safety, convenience, efficacy, and insurance restrictions are among the factors considered. Patient prognostic profile is also used to guide initial DMT selection including demographic, clinical, and imaging characteristics that help predict disease severity. Potential predictors of severity include male gender, early progressive disability, poor relapse recovery, high burden of disease on MRI, or frequent early attacks[6].

The desired DMT chosen by the patient and provider through shared decision-making fits into one of two treatment paradigms for initial DMT treatment, starting with low efficacy therapy or starting with high efficacy therapy. Providers vary in their approach, although most agree that patients with highly active disease or unfavorable prognosis should start high-efficacy disease modifying therapy for MS[7, 8]. A limited number of randomized controlled trials and observational studies have suggested that the majority of infusion DMTs, including ocrelizumab and natalizumab, have the highest efficacy, followed by oral DMTs, such as fingolimod, with intermediate efficacy and the lowest efficacy is seen in the injectables of which interferon beta and glatiramer acetate are the most common[6, 9-11]. A caveat to this is the recent approval of the injectable Ofatumumab who was found to be associated with lower annualized relapse rates compared to the oral agent teriflunomide[9].

Access to high-efficacy DMTs is affected by health insurance coverage[3]. These DMTs are often more expensive than injectables with lower-efficacy profiles. For this reason, insurance companies have adopted step therapy approaches to MS treatment, in which patients are required to fail a cheaper DMT before pursuing a more costly, often higher efficacy, DMT. Although this approach is seen as cost-effective, there is no data to support a specific sequencing schema for MS treatment. This practice has continued largely due to the growing costs of MS treatment, irrespective of the growing number of approved DMTs. It has been reported that DMTs increase in price above the level of inflation after entering the US market[12-14]. This is contrary to other drug categories that decrease in price after entering a competitive drug market. These trends in DMT prices continue to drive healthcare costs among persons with multiple sclerosis and result in reduced adherence and access to DMTs[14].

This study aims to evaluate the financial limitations and insurance restrictions experienced by patients pursuing disease modifying therapy for multiple sclerosis and how the approach to choosing treatment for MS is affected.

Methods:

A retrospective chart review of patients seen in the multiple sclerosis (MS) specialty clinic at Alfred Taubman Health Care Center of Michigan Medicine between January 1st 2020 and February 29th 2020 was performed. Adult patients with a diagnosis of MS based on the 2017 McDonald Criteria were included in the study[15].

A diagnosis of MS was made when CNS lesions were shown to be both disseminated in space and disseminated in time and no other non-MS diagnosis better explained the clinical presentation. Dissemination in space was defined as 2 clinical attacks involving lesions in different CNS sites or MRI evidence of ≥1 T2 lesion ≥2 of the following typical CNS sites affected: periventricular, cortical/juxtacortical, infratentorial and spinal cord. Dissemination in time was defined as 2 clinical attacks involving lesions in the CNS, MRI showing gadolinium enhancing and nonenhancing typical MS lesions simultaneously, new T2 lesion or gadolinium enhancing typical MS lesion compared to baseline, or CSF oligoclonal bands[15]. Relapsing-remitting MS was defined as an MS course with clearly defined relapses with partial or full recovery. Primary progressive MS was defined as an MS course characterized by at least one year of insidious neurological progression irrespective of clinical relapse[16]. Secondary progressive MS was characterized as an initial relapsing-remitting MS course followed by a gradual persistent worsening with or without additional clinical relapses. Clinically isolated syndrome was defined by a clinical attack with objective evidence of one or more lesions requiring additional evidence of dissemination in time and/or dissemination in space[17].

Medical records were accessed electronically on the medical-record software Epic. Data was collected from results of diagnostic tests, notes from health care providers and denial letters from insurance companies.

Descriptive statistics were calculated using the statistical software IBM SPSS statistics. A chi-square test was used to compare categorical data. T-tests were used to compare means and a z-score test was used to test for statistically significant differences in gender. Alpha was set at 0.05 with a significance level of $p<0.05$ for statistical significance testing.

Ethical approval and exemption from ongoing IRB review was obtained by the Institutional Review Board at the University of Michigan.

Results:

During the 2-month study period, a total of 460 patients were evaluated in the MS specialty clinic by 5 neurologists specialized in MS. Of the 460 patients, 78 (17.0%) did not carry a diagnosis of MS or CIS (Figure 1). Among the non-MS diagnoses seen, were probable neurosarcoidosis, possible lupus cerebritis, autoimmune encephalitis, migraine, central nervous system vasculitis, and neuromyelitis optica spectrum disorders. Of the additional 382 patients, 32 (8.4%) were diagnosed with CIS. The remaining 350 (91.6%) patients carried a diagnosis of MS.

Among the patients with MS, relapsing-remitting was the most common subtype with 287 (82.0%) patients; 22 (6.3%) patients had primary progressive MS, and the remaining 41 (11.7%) had secondary progressive MS (Table 1). No patients had progressive relapsing MS. Female patients made up the majority of the study population with 254 (72.6%) patients. White patients accounted for 295 (84.3%) while black patients made up 30 (8.6%), and the remaining 25 (7.1%) patients did not report race. Of the study population, 333 (95.1%) reported Non-

Hispanic as their ethnicity, while 6 (1.7%) reported Hispanic and the remaining 11 (3.1) did not report ethnicity. Report of marital status revealed 167 (47.7%) patients were married at the time of data collection while 78 (22.3%) were reportedly single. The remaining 105 patients were divorced, legally separated, widowed or marital status was unknown. The mean age at time of MS diagnosis was 39.1 years (s.d. ±11.9) and the mean age at time of clinic visit during the study was 49.4 years (s.d. ±12.7). Of the patients with insurance, 203 (58%) had private insurance while 145 (41.5%) had public insurance in the form of Medicaid and/or Medicare. Only 2 (0.6%) patients did not have insurance at the time of data collection. Concerning DMT history, 265 (75.7%) patients were on a DMT for MS during the study period with a mean number of total DMTs throughout the course of their MS of 2.01 (s.d. ±1.5, range 0-9), and a mean time from diagnosis to start of DMT of 4.73 months (s.d. ±9.10). Mean age at diagnosis was defined as age at the time of the clinical appointment at which point the patient satisfied the McDonald Criteria and the diagnosis of MS was given. Mean time from diagnosis to start of DMT was defined as the time from the date of diagnosis of MS, as defined above, to the start of their first DMT. The study population was found to be representative of the MS population in the US[18].

Of the 350 patients with MS, 72 patients were unable to start and/or continue their desired DMT, as agreed upon by the provider and patient, at some point during their treatment course due to financial limitations related to their insurance coverage. These patients were identified upon review of DMT history, inclusion of financial difficulties within notes by health care providers and/or by identification of insurance denial letters in their medical records. Patients without mention of financial limitations or with difficulty accessing DMTs for non-financial reasons were not included in this smaller subset of patients.

Among these 72 patients, 9 patients experienced financial limitations with 2 different DMTs, making up 81 occurrences in which DMTs were inaccessible to patients secondary to insurance coverage. Among the DMTs rejected by insurance companies or discontinued were alemtuzamab, beta-Interferon-1a/1b, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, ocrelizumab, rituximab, and teriflunomide (Table 2). Glatiramer acetate and dimethyl fumarate were the most common DMTs patients were unable to access with 14 (17.3%) patients each, followed by Ocrelizumab (n=13, 16.0%), beta-interferon 1a (n=10, 12.3%) and natalizumab (n=9, 11.1%). DMTs with an infusion-based route of administration was most likely to experience insurance restrictions with 29 (35.8%) occurrences, followed by oral DMTs and injectables with 26 (32.1%) occurrences each.

Among the reasons for the delay, rejection or lack of insurance coverage for these DMTs were required step therapy approach to treatment, high copays, insurance denial due to lack of FDA approval for MS subtype, CIS or pregnancy, a reduction or loss of insurance coverage or DMT was not on the insurance formulary (Figure 1, Table 2). For a significant number of occurrences, the specific financial difficulty was unspecified (n=33, 40.7%). The most common reason for a delay, rejection or lack of insurance coverage for a DMT was the requirement by insurance companies to adopt a step therapy, or “fail first”, approach to treatment, often consisting of injectables as first line, followed by oral medications, before starting infusion therapy (n=16,

19.8%). This was followed by a change or loss of insurance (n=15, 18.5%) and high copays (n=6, 7.4%) (Figure 1) of up to 3000/mo. Patients experienced most of these insurance difficulties at the initiation of treatment with DMTs (65.8%). At some point during their disease course, 46 (63.9%) of these patients were off DMT due to financial reasons related to insurance coverage, making up 12.1% of the entire MS study population. Of these 46 patients, 2 patients remained treatment naïve, at the time of the study, after experiencing insurance denials for infusion therapy because both infusion DMTs were part of a step therapy program both patients were unable to satisfy due to severe trypanophobia.

The DMTs requiring a step therapy approach were either oral or infusion-based therapies requiring injectables and/or oral DMTs prior to initiation. The oral therapies requiring step therapy prior to insurance approval included dimethyl fumarate, teriflunomide, and fingolimod. The infusion therapies that participated in step therapy programs among insurance companies included ocrelizumab, natalizumab, and alemtuzumab. Insurance policies differed in their approach to step therapy with some specifying failure of one injectable and one oral DMT prior to approval of an infusion DMT while others indicated failure of 1, 2 or 3 alternative DMTs prior to approval. For insurance approval of dimethyl fumarate, failure or adverse reaction to the following injectables was required: avonex, glatiramer acetate, betasaron, and mitoxantrone or failure or adverse reaction to the oral DMT fingolimod. For insurance approval of teriflunomide, failure or adverse reaction to the injectables beta-interferon-1a/1b, glatiramer acetate or oral agent dimethyl fumarate was required. For insurance approval of fingolimod, failure or adverse reaction to beta-interferon-1a, glatiramer acetate was required. For insurance approval of Ocrevus, failure or adverse reaction to the injectables glatiramer acetate, beta-interferon-1a/1b and/or the oral DMTs fingolimod, dimethyl fumarate or teriflunomide was required. For insurance approval of natalizumab, failure or adverse reaction to the injectables beta-interferon-1a/1b, peginterferon beta-1a glatiramer acetate, and/or the oral DMTs fingolimod and dimethyl fumarate were required. Finally, for insurance approval of alemtuzumab, failure or adverse reaction to any oral DMT was required.

Of the 16 occurrences in which a step therapy requirement prevented the patient and provider from choosing their desired DMT, 7 patients successfully pursued either glatiramer acetate or interferon beta 1a/1b instead of their desired ocrelizumab or natalizumab infusion. After insurance denial for natalizumab, 1 patient received rituximab treatment instead. The 2 patients who were denied fingolimod successfully pursued glatiramer acetate. The 1 patient whose insurance rejected teriflunomide, successfully pursued dimethyl fumarate. The 4 patients who were denied dimethyl fumarate successfully received treatment with glatiramer acetate or interferon beta 1a/1b. The 1 patient who was denied alemtuzumab by their insurance company has remained off DMT for MS completely.

The original 350 patients with MS were split into two study groups for further analysis to detect differences between the groups that would account for differences in access to DMT for MS. The “No Insurance-related restrictions Group” consisted of the 278 patients who were able to start and continue their desired disease modifying therapy as agreed upon by the provider and patient. The “Insurance-Related Restrictions Group” was defined as the 72 MS patients who

were unable to start and/or continue their desired DMT, as agreed upon by the provider and patient, due to financial reasons related to their insurance coverage (Table 1). When comparing the two study groups, a statistically significant difference was found in the type of insurance, with the patients in the Insurance-Related Restrictions group more likely to benefit from public insurance (N=37, 51.4%) compared to the No Insurance-Related Study Group (N=108, 38.8%) (p=.045). The Insurance-Related Restriction Group was also more likely to be single (N=24, 33.3%) compared to the opposing study group (N=54, 19.4%) (p=.013) and more likely to be younger at the time the study was conducted with a mean age of 45.17 years (s.d.$\pm$ 11.796) compared to the No Insurance-Related Study Group with a mean age of 50.45 years (s.d.$\pm$12.755) (p=.002). There was no difference in gender, race, ethnicity, age at diagnosis, clinical course, mean time from diagnosis to start of DMT, or mean number of DMTs tried (Table 1).

Among the two study groups, over 21 different DMTs were used to treat MS. The most common DMT used among this 350 patient study population was glatiramer acetate with 171 (48.9%) patients. The second most popular DMT was Interferon beta-1a with 142 (40.6%) patients, followed by dimethyl fumarate with 92 (26.3%) patients, ocrelizumab with 86 (24.6%) patients and natalizumab with 55 (15.7%) patients. The remaining therapies included alemtuzamab, dioximel fumarate, fingolimod, interferon-beta-1b, azathioprine, belimumab, cyclophosphamide, methotrexate, mitoxantrone, peginterferon beta-1a, rituximab, siponimod, and teriflunomide. Additional therapies included extracorporeal photopheresis, hematopoietic stem cell transplant, and monthly pulse prednisone. The insurance-Related Restrictions group appeared to be more likely to initiate DMT for MS with glatiramer acetate (N=30, 41.7%) compared to the No Insurance-Related Restrictions group (N=93, 33.5%), although both groups had similar experience with this DMT with ~50% of each group experiencing glatiramer acetate at some point during their MS course. The No-Insurance-Related Restrictions group appeared to be more likely to initiate DMT for MS with ocrelizumab (N=20, 7.2%) compared to the Insurance-Related Restrictions group (N=2, 2.8%) (Table 1).

Discussion:

In this study of 350 patients with multiple sclerosis, we found that although the majority benefited from health insurance (99.4%), approximately 1 in 5 experienced difficulty accessing disease modifying therapies due to insurance limitations. We also found that the financial burdens resulting from these insurance restrictions reduced the ability of patients with MS to adhere to therapy with 63.9% (46/72) of these patients (12.1% of the total MS population) unable to continue on a DMT at some point during their MS course. This data suggests a gap between health insurance needs and current coverage.

Inability to continue on disease modifying therapies for MS due to high copays has been reported previously and continues to serve as a barrier to access[1, 3]. Of the 72 patients experiencing financial difficulties, 7.6% (n=6) were unable to continue on their current DMT because their copays were too high, with subjective reports of up to $3000 a month in copay requirements. Although high copays are not unique to MS therapies, the economics of MS treatment differs from that of most other drug categories in that price inflation and lack of

price transparency in a monopolistic competitive market has fostered rapidly increasing DMT prices despite the continued addition of new DMTs[19]. Regulatory structures are lacking and should be put in place to further control the rising prices of MS therapies.

This study found that patients who experienced insurance restrictions while pursuing DMTs for MS were more likely to benefit from public insurance in the form of Medicare and Medicaid compared to MS patients who did not experience insurance restrictions. This is unexpected given that Medicaid patients are required to receive the lowest drug prices available through the Medicaid Drug Rebate Program. However, this association may be due to the inability of patients benefiting from government-funded health care to have access to patient assistant programs because of federal antikickback laws[19]. Medicaid, like private insurers, also enforce restrictive insurance policies regarding MS therapies with 2 examples found in this study in which patients had to switch from brand name glatiramer acetate to generic after switching from private insurance to Medicaid.

The high prices of DMTs has forced patients and providers to abandon shared decision making based on patient preferences and clinical data for adherence to step therapy requirements enforced by insurance companies. At least 16 of our patients reported an inability to access their desired DMT due to step therapy requirements. These requirements did not take into account the presumed MS severity or prognostic factors of the patient for which studies have shown that patients with severe prognostic profiles should initiate high efficacy DMT to reduce the number or clinical and/or radiographic activity. Step Therapy assumes a one size fits all approach to MS treatment with low efficacy DMTs as first line and oral or infusion therapies as second/third line with no evidence to support this practice. Insurance policies should eliminate step therapy programs to further increase access to DMTs for patients with MS, while further research is needed to identify the patients that would most benefit from low-efficacy vs intermediate efficacy vs high efficacy DMTs.

Limitations:

The results of this study should be analyzed within the context of the following limitations. Patients who experienced insurance restrictions while pursuing disease modifying therapies for MS were identified via notes from health care providers and insurance denial letters scanned into their medical records. Given that some insurance denial letters may not have been incorporated into a patient's medical record or a health care provider may have excluded financial barriers to access to disease modifying therapies, this study may have underestimated the number of patients who experienced insurance restrictions in their pursuit of MS treatment. Given that only 150 of the 350 MS patients evaluated in this study received all of their MS treatment at Michigan Medicine, the remaining 200 patients may have experienced financial difficulties accessing disease modifying therapies that were not reported in their medical record prior to transferring their care, further underestimating the true impact of financial barriers on access to disease modifying therapies. Further, the use of free or discounted drug programs that help mitigate out-of-pocket drug expenses was infrequently reported in patient medical records and may have underestimated the number of patients

experiencing financial difficulties. These limitations along with the retrospective study design may have resulted in misclassification bias.

Conclusion:

One in five patients with MS were found to experience difficulty accessing DMTs secondary to insurance restrictions, and 12.1% of the MS population were off DMT completely at some point during their MS course. Step therapy as a required approach to treatment was the most common barrier to desired DMT treatment. Financial barriers to DMT use secondary to insurance restrictions experienced by patients with MS should be further elucidated and alleviated by both insurance and drug companies.

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Figure 1: Study Population Diagnoses and Insurance-related Restrictions

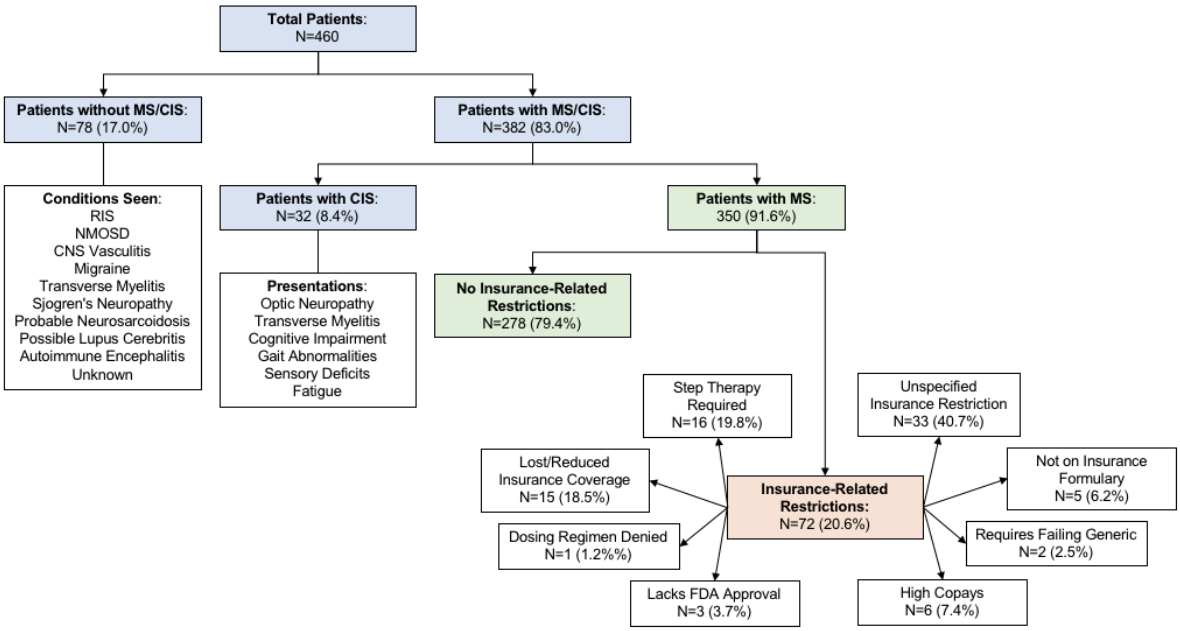

Table 1: Characteristics of Multiple Sclerosis Study Population

Categories	Total MS (n = 350)	No Insurance-related Restrictions Group (n = 278)	Insurance-related Restrictions Group (n = 72)	Significance Testing
Gender (n, %)				Z= 1.8528
Female	254 (72.6%)	208 (74.8%)	46 (63.9%)	P= .06432
Race (n, %)				Chi Square statistic=0.116
White	295 (84.3%)	234 (84.2%)	61 (84.7%)	P=.733
Black	30 (8.6%)	23 (8.3%)	7 (9.7%)	
Other/Unknown	25 (7.1%)	21 (7.5%)	4 (5.6%)	
Ethnicity (n,%)				Chi Square statistic=1.533
Non-Hispanic	333 (95.1%)	265 (95.3%)	68 (94.4%)	P=.216
Hispanic	6 (1.7%)	6 (2.2)	0 (0%)	
Unknown	11 (3.1%)	7 (2.5%)	4 (5.6%)	
Mean Age (years)	49.36 (min 18, Max 79) Sd 12.728,	50.45 (Min 18, Max 79) Sd 12.755	45.17 (Min 26, Max 74) Sd 11.796	**P=.002**
Mean Age at Diagnosis (years)	39.10 (min 12, Max 71) Sd 11.947	39.70 (min 16, Max 71) Sd 12.080	37.14 (Min 12, Max 70) Sd 11.451	P=.269
Insurance Type (n, %)				
Private	203 (58.0%)	169 (60.8%)	34 (47.2%)	Chi Square statistic=4.005
Public	145 (41.4%)	108 (38.8%)	37 (51.4%)	**P=.045**
None	2 (0.6%)	1 (0.4%)	1 (1.4%)	
Marital Status (n,%)				
Single	197 (22.3%)	54 (19.4%)	24 (33.3%)	Chi Square statistic=6.235
Married	167 (47.7%)	139 (50.0%)	28 (38.9%)	**P=.013**
Divorced	18 (5.1%)	13 (4.7%)	5 (6.9%)	
Legally Separated	3 (0.9%)	1 (0.4%)	2 (2.8%)	
Widow	8 (2.3%)	4 (1.4%)	4 (5.6%)	
Unknown	76 (21.7%)	67 (24.1%)	9 (12.5%)	
Clinical Course (n,%)				
Relapsing Remitting	287 (82.0%)	220 (79.2%)	67 (93.1%)	Chi Square statistic =
Primary Progressive	22 (6.3%)	20 (7.2%)	2 (2.8%)	7.938
Secondary Progressive	41 (11.7%)	38 (13.6%)	3 (4.2%)	P=.094
Mean time from diagnosis to start of DMT (months)	4.73 Sd 9.106	4.86 Sd 10.022	4.37 Sd 6.058	P=0.6726
On DMT (n, %)	265 (75.7%)	207 (74.5%)	58 (80.6%)	
Mean number of DMTs	2.01 (Min 0, Max 9), Sd 1.498,	2.01 (min 0, Max 9) Sd 1.571	2.04 (Min 0, Max 5) Sd 1.192	P=0.863

Table 2: Disease Modifying Therapies with insurance-related restrictions experienced by study population

Disease Modifying Therapy (Route of administration)	**Total Occurrences N = 81**	**Insurance-Related Restrictions**	
Glatiramer Acetate (Injectable)	14 (17.3%)	• Required Failing Generic prior to starting brand name • Lost/Reduced Insurance Coverage • Not on insurance formulary • Dosing Regimen Denied • High Copays • Lacks FDA approval for MS Subtype, CIS or use in pregnancy • Unspecified Insurance Limitation	N=2 (14.3%) N=2 (14.3%) N=2 (14.3%) N=1 (7.1%) N=1 (7.1%) N=1 (7.1%) N=5 (35.8%)
Dimethyl fumarate (Oral)	14 (17.3%)	• Lost/Reduced Insurance Coverage • Step Therapy Required • High Copays • Not on insurance formulary • Unspecified Insurance Limitation	N=4 (28.6%) N=4 (28.6%) N=2 (14.3%) N=1 (7.1%) N=3 (21.4%)
Ocrelizumab (Infusion)	13 (16.0%)	• Step Therapy Required • Unspecified Insurance Limitation	N=5 (38.5%) N=8 (61.5%)
Beta-Interferon-1a (Injectable)	10 (12.3%)	• Lost/Reduced Insurance Coverage • High Copays • Not on insurance formulary • Unspecified Insurance Limitation	N=4 (40%) N=2 (20%) N=1 (10%) N=3 (30%)
Natalizumab (Infusion)	9 (11.1%)	• Step Therapy Required • Lacks FDA approval for MS Subtype, CIS or use in pregnancy • Lost/Reduced Insurance Coverage • Unspecified Insurance Limitation	N=3 (33.3%) N=1 (11.1%) N=1 (11.1%) N=4 (44.5%)
Teriflunomide (Oral)	6 (7.4%)	• Lost/Reduced Insurance Coverage • Step Therapy Required • Unspecified Insurance Limitation	N=1 (16.7%) N=1 (16.7%) N=4 (66.6%)
Fingolimod (Oral)	6 (7.4%)	• Step Therapy Required • Lost/Reduced Insurance Coverage • Unspecified Insurance Limitation	N=2 (33.3%) N=2 (33.3%) N=2 (33.3%)
Rituximab (Infusion)	5 (6.2%)	• Lost/Reduced Insurance Coverage • Lacks FDA approval for MS Subtype, CIS or use in pregnancy • Unspecified Insurance Limitation	N=1 (20%) N=1 (20%) N=3 (60%)
Alemtuzamab (Infusion)	2 (2.5%)	• Step Therapy Required • Unspecified Insurance Limitation	N=1 (50%) N=1 (50%)
Beta-Interferon-1b (Injectable)	2 (2.5%)	• Not on insurance formulary • High Copays	N=1 (50%) N=1 (50%)

Table 3: Disease Modifying Therapies at initiation of DMT use and throughout disease course

Disease Modifying Therapy	**Total MS Group (n = 350)**	**First DMT No Insurance-related Restrictions Group[1] (n = 278)**	**All DMTs No Insurance-related Restrictions Group[1] (n = 278)**	**First DMT Insurance-related Restrictions Group[2] (n = 72)**	**All DMTs Insurance-related Restrictions Group[2] (n = 72)**
Injectable					
Glatiramer acetate (Copaxone,Glatopa)	171 (48.9%)	93 (33.5%)	135 (48.6%)	30 (41.7%)	36 (50%)
Interferon beta-1a (Avonex, Rebif)	142 (40.6%)	70 (25.2%)	112 (40.3%)	20 (27.8%)	30 (41.7%)
Interferon beta-1b (Betaseron)	22 (6.3%)	15 (5.4%)	20 (7.2%)	1 (1.4%)	2 (2.8%)
Peginterferon beta-1a (Plegridy)	3 (0.9%)	1 (0.4%)	3 (1.1)	0 (0%)	0 (0%)
Oral					
Dimethyl fumarate (Tecfidera)	92 (26.3%)	19 (6.8%)	68 (24.5%)	5 (6.9%)	24 (33.3%)
Fingolimod (Gilenya)	43 (12.3%)	7 (2.5%)	33 (11.9%)	1 (1.4%)	10 (13.9%)
Teriflunomide (Aubagio)	28 (8%)	5 (1.8%)	22 (7.9%)	3 (4.2%)	6 (8.3%)
Siponimod (Mayzent)	4 (%)	1 (0.4%)	4 (1.1)	0 (0%)	0 (0%)
Methotrexate	2 (0.6%)	0 (0%)	1 (0.4%)	0 (0%)	1 (1.4%)
Diroximel fumarate (Vumerity)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)
Azathioprine (Imuran)	1 (0.3%)	1 (0.4%)	1 (0.4%)	0 (0%)	0 (0%)
Infusion					
Ocrelizumab (Ocrevus)	86 (24.6%)	20 (7.2%)	70 (25.2%)	2 (2.8%)	16 (22.2%)
Natalizumab (Tysabri)	55 (15.7%)	5 (1.8%)	45 (16.2%)	3 (4.2%)	10 (13.9%)
Rituximab (Rituxin)	26 (7.4%)	4 (1.4%)	19 (6.8%)	4 (5.6%)	7 (9.7%)
Cyclophosphamide (Cytoxane)	7 (2.0%)	1 (0.4%)	6 (2.1%)	1 (1.4%)	1 (1.4%)
Mitoxantrone (Novantrone)	7 (2.0%)	1 (0.4%)	5 (1.8%)	0 (0%)	2 (2.8%)
Alemtuzamab (Lemtrada)	4 (1.1%)	0 (0%)	3 (1.1)	0 (0%)	1 (1.4%)
Belimumab (Benlysta)	1 (0.3%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)