Original Article

Assessment of treatment patterns associated with injectable disease-modifying therapy among relapsing–remitting multiple sclerosis patients

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Abstract

Background: Availability of oral disease-modifying therapy (DMT) for relapsing–remitting multiple sclerosis (RRMS) may affect injectable DMT (iDMT) treatment patterns.

Objective: The objective of this paper is to evaluate iDMT persistency, reasons for persistency lapses, and outcomes among newly diagnosed RRMS patients.

Methods: Medical records of 300 RRMS patients initiated on iDMT between 2008 and 2013 were abstracted from 18 US-based neurology clinics. Eligible patients had ≥3 visits: pre-iDMT initiation, iDMT initiation (index), and ≥1 visit within 24 months post-index. MS-related symptoms, relapses, iDMT treatment patterns (i.e. persistency, discontinuation, switching, and restart), and reasons for non-persistency were tracked for 24 months.

Results: At 24 months, iDMT persistency was 61.0%; 28.0% of patients switched to another DMT, 8.0% discontinued, and 3.0% stopped and restarted the same iDMT. The most commonly identified reasons for non-persistency were perceived lack of efficacy (22.2%), adverse events (18.8%), and fear of needles/self-injecting (9.4%). At 24 months, 38.0% of patients had experienced a relapse and 11.0% had changes in MRI lesion counts. Patients without MS-related symptoms at index reported increases in the incidence of these symptoms at 24 months.

Conclusions: Non-persistency with iDMT remains an issue in the oral DMT age. Many patients still experienced relapses and disease progression, and should consider switching to more effective therapies.

Introduction

Injectable disease-modifying therapies (iDMTs) used in the treatment of relapsing–remitting multiple sclerosis (RRMS) include the intramuscular (IM) or subcutaneous (SC) beta-interferons (IFN) 1a or 1b and glatiramer acetate.[1] These agents have been shown to reduce the annualized relapse rate by approximately 30%, and have a modest benefit in the prevention of disability progression.[2–6] Small differences in efficacy have been demonstrated among these iDMT agents.[7]

Previous research suggests that some patients receiving iDMT may have poor adherence and/or persistency. In a retrospective cohort pharmacy claims study of 1891 MS patients, approximately half of patients discontinued iDMT within one year of treatment initiation.[8] In a systematic review of iDMT observational and randomized controlled trials, adverse events and lack of efficacy were the most commonly cited reasons for discontinuation.[9] Another common reason for discontinuation was injection site reactions.[9] Notably, psychological issues related to frequent injections, such as needle phobia, also appeared to play a role in the decision to discontinue treatment. In a prospective, randomized, open-label study comparing persistency and patient satisfaction between fingolimod and iDMT, 90.5% of patients randomized to iDMTs switched treatments within one year, mainly for injection-related

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reasons.[10] Retention to randomized treatment with iDMT was 29.2% and with fingolimod was 81.3% after one year.[10]

Several ''real-world'' observational studies or retrospective database analyses have examined the persistence and discontinuation of iDMTs.[11–23] However, most of these studies were conducted using data from single-centers and/or the studied time periods were before the availability of oral DMTs (2010). The approval of oral DMTs has provided patients with RRMS a viable alternative route of administration for DMT beyond infusions or injections. The availability of these agents has been shown to influence iDMT treatment patterns;[24] therefore, studies to examine iDMT persistency, switching, and discontinuation that include the time period after the introduction of oral DMTs are warranted. The objective of this analysis was to provide insight into iDMT treatment patterns (persistency, discontinuation, switching, and restarts), identify reasons for therapy change, and identify RRMS-specific outcomes based on a retrospective review of the medical records of a subset of patients in the United States (US) with RRMS.

Methods

Study overview

This study was a retrospective medical record review of a sample of patients from neurology practice sites across the US. The full timeframe for this study was from January 2008 through August 2015, with the patient identification period occurring between August 2008 and August 2013. The first patient visit for which treatment initiation with iDMT was recorded was defined as the index visit. The iDMTs evaluated were IM IFN β-1a (Avonex®, Biogen, Cambridge, MA), SC IFN β-1a (Rebif®, EMD Serono Inc, Rockland, MA), SC IFN β-1b (Betaseron®, Bayer AG, Leverkusen, Germany), and glatiramer acetate (Copaxone®, Teva Neuroscience, Kansas City, MO). Patients were followed for 24 months after iDMT initiation even if they discontinued treatment with iDMT agents. All data were de-identified. This study was approved by the Sterling centralized institutional review board (Atlanta, GA), and patient consent waivers were obtained before the study was initiated.

Site selection

Study sites were chosen based on a review of a prescriber report provided by IMS Health (Danbury, CT), study sponsor recommendations, and prior RRMS study participating sites as identified by the medical record abstraction data vendor. The criteria for site selection were based on the geographic distribution of disease prevalence, level of specialization (i.e. general neurology, academic-affiliated institutions, and MS specialty neurologists), and results from a pre-qualification/screening questionnaire. Sites were selected to ensure geographic balance based on prevalence, a mix of levels of specialization, and ability/willingness to respond to chart requests. Each site was invited to complete a detailed questionnaire to better understand site characteristics and RRMS treatment experience as well.

Patient selection

Eligible patients were those with RRMS who initiated iDMT within six months of diagnosis, who had at least one pre-index visit, and had subsequent post-index visits (≥1 visit) for up to 24 months after the index visit. Patients were required to have at least 24 months of follow-up post-index, irrespective of treatment status with iDMT. Patients initiating treatment with any DMT other than those specified for this analysis or with any evidence of prior iDMT use in the six months before the index visit were excluded. Patients with missing age or sex information were also excluded.

Information collected from medical records

The medical record reviewers were nurses or pharmacists with medical record experience in neurology. The reviewers were trained on the study's design, intent, key variable definitions, data collection process/reporting, and adverse event reporting. Standardized data collection forms were used. Baseline patient demographics, comorbidities, and MS disease status were tracked in the pre-index period. Treatment patterns for each patient were tracked at distinct time windows of 3, 6, 9, 12, 18, and 24 months post-index. The tracked treatment patterns were discontinuation, switching to another DMT agent, or a restart of the original iDMT after a short hiatus. Assignment to switch, discontinuation, and restarts were mutually exclusive. Discontinuation was defined as medical record documentation of index iDMT discontinuation within the cumulative time window, with no subsequent recorded use of the discontinued agent. Switching was defined as medical record documentation of index iDMT discontinuation, followed by another documentation indicating the start of a different DMT for RRMS within the cumulative time window. Both forward and backward switch events were captured. Forward switching was defined as the switch to another DMT for RRMS within the cumulative time window, whereas backward switching was a

forward switch to another DMT, followed by switching back to the index iDMT within that same time window. A restart was defined as medical record documentation of index iDMT stop or discontinuation within the cumulative time window, with subsequent documentation of restarting the index iDMT after at least 30 days.

Reasons for any of the treatment pattern changes as recorded in the physician notes in the medical record were tracked over the same time period. Captured reasons are listed in Supplemental Table E1. Indicators of disease progression were also tracked at the pre-index and index visits to serve as a baseline, as well as over the distinct time windows of 3, 6, 9, 12, 18, and 24 months post-index. These indicators included magnetic resonance imaging (MRI) evidence of new lesions or more extensive demyelination, and physician narratives of worsening visual disturbance, bowel incontinence, neurological symptoms, and gait or mobility impairment based on physical exam. Relapse episodes were tracked over the distinct time windows of 3, 6, 9, 12, 18, and 24 months post-index and were defined as any record or an office visit, emergency department/urgent care visit, or hospitalization followed by medical record documentation of corticosteroid use within seven days of the event. In addition, any notation by the physician in the medical record of a confirmed relapse event, regardless of corticosteroid intervention, was counted as a relapse episode.

Data analysis
This study was primarily descriptive. Raw counts or percentages were calculated for categorical variables. Means, standard deviations, and medians were calculated for continuous variables. Data were analyzed cumulatively (0–3 months, 0–6 months, etc.) and by time interval (0–3 months, 4–6 months, etc.). Overall persistency was determined by the proportion of patients still being treated with the index iDMT at post-index cumulative time windows. The median censor-adjusted time to switch and median censor-adjusted time to discontinuation were computed. All analyses were conducted using SAS version 9.4 statistical software (Cary, NC).

Results

Study sites and patients
A total of 300 distinct medical records were abstracted from 18 US-based neurology clinics. The majority of the prescribing physicians were general neurologists in small or solo practices; most had ≥10 years of experience. The proportion of patients initiating each drug on the index date was 34% for glatiramer acetate, 31% for IM IFN β-1a, 21% for SC IFN β-1a, and 14% for SC IFN β-1b. The average age of the patients was 42 years and 74% were women (Table 1). The largest proportion of patients were from the Midwest region (44%), whereas only 4% of all patients were from the Western region of the US.

Treatment patterns
During the 24 months of follow-up, nearly one-third (28.0%) of patients had switched treatments; 8.0% had discontinued treatment, and 3.0% stopped and restarted the same iDMT, for a total non-persistency rate of 39.0% (Figure 1(a)). The overall persistency rate on iDMT medications declined from 91.3% at 3 months to 61.0% at 24 months from the time of initiation (Figure 2). Treatment switches occurred most frequently in the first three months of treatment, whereas discontinuations occurred later (Figure 1(b)). The median time to switch was 288 days and median time to discontinuation was 401 days. When patients switched treatment from the

Table 1. Demographics of iDMT patients.

Characteristic	Total	Glatiramer acetate	IM IFN β-1a	SC IFN β-1a	SC IFN β-1b
Number of patients, (%)	300 (100)	103 (34)	94 (31)	62 (21)	41 (14)
Female, %	74	77	77	66	71
Mean age, years ± SD	42 ± 12	44 ± 12	41 ± 12	40 ± 11	39 ± 13
Region, %					
Midwest	44	39	44	53	42
Northeast	17	14	26	18	2
South	36	44	29	26	46
West	4	4	2	3	10

iDMT: injectable disease-modifying therapy; IFN: interferon; IM: intramuscular; SC: subcutaneous.
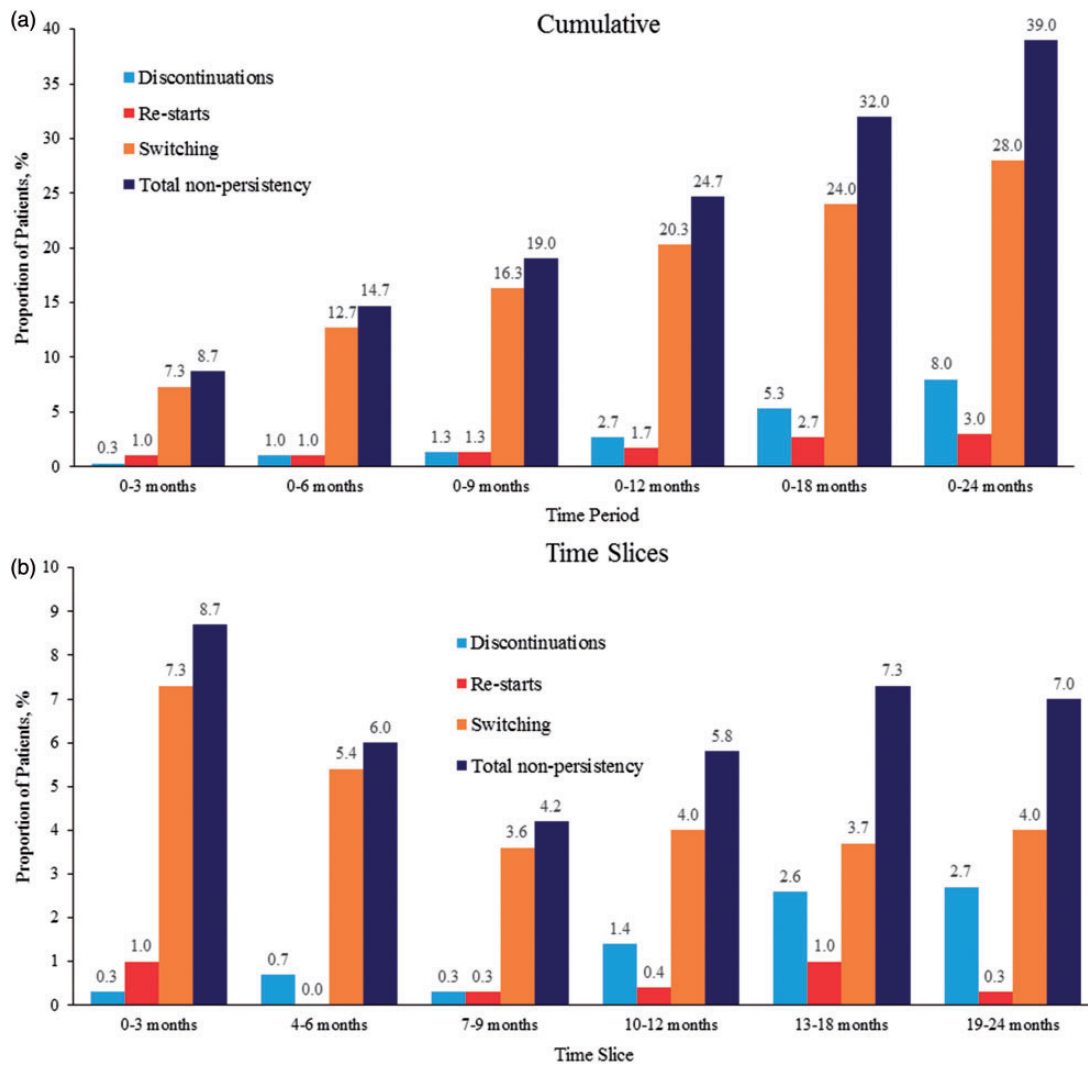
Figure 1. Proportion of patients with injectable disease-modifying therapy who were non-persistent, broken down into discontinuations, restarts, or switches (a) cumulatively over time and (b) over distinct time slices.
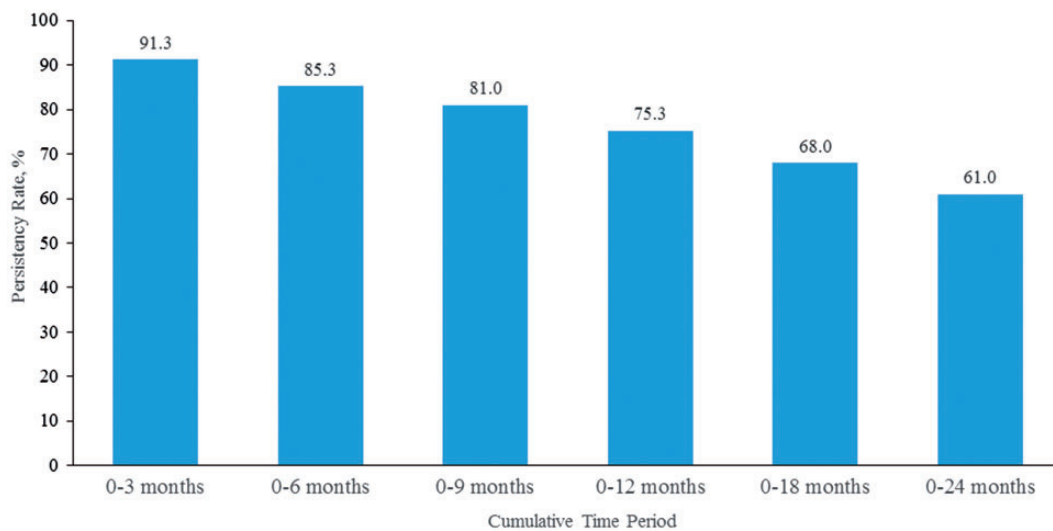

Figure 2. Persistency rate of index injectable disease-modifying therapy over time.

index iDMT, the switch was relatively evenly distributed to iDMTs, oral DMTs, and natalizumab (Figure 3).

The most commonly identified reasons for non-persistency over the 24-month period were perceived lack of efficacy (22.2%), adverse events (18.8%), and fear of needles/self-injecting (9.4%; Figure 4). These same reasons were the most common reasons for non-persistency over the 0- to 6-month and 0- to 12-month periods. Although the study was not designed or powered to detect differences between persistent and non-persistent patients, the baseline characteristics of non-persistent patients were generally similar to persistent patients. However, non-persistent patients tended to be younger (mean age 39.9 vs 42.9 years, respectively; $p = 0.04$), require mobility assistance (crutch/cane/walker; $p = 0.05$), and have a greater incidence of tremors (12.8% vs 4.9%, respectively; $p = 0.01$).

Clinical outcomes
Physician-reported MRI-verified disease progression by month 24 was common. In all, 20.7% of patients had disease progression based on MRI evidence of new/enlarged lesions, 11.0% had a change in lesion count, and 8.3% had a change in level of brain atrophy. The percentage of patients experiencing a relapse increased over time from 30.7% at 12 months to 38.0% at 24 months. The average

number of relapses increased from 0.42 (standard deviation = 0.73) at 12 months to 0.54 (standard deviation = 0.88) at 24 months. Patients who did not have MS-related symptoms at index reported increases in the incidence of these symptoms at 24 months (Figure 5).

Although the study was not powered to determine differences between non-persistent and persistent patients, a greater percentage of non-persistent patients had experienced a relapse compared with persistent patients at 24 months. Furthermore, non-persistent patients had a higher relapse rate, a higher percentage of patients with MRI disease progression (e.g. new/enlarged lesions, changes in lesion count, and a change in level of brain atrophy), and had a greater increase in the incidence of symptoms compared with persistent patients (Supplemental Table E2).

Discussion
This real-world medical chart review revealed that after initiating iDMT for RRMS, overall persistency decreased over time with 75% of patients persistent after 12 months and 61% persistent after 24 months. The most common reason for loss of persistency was switching to another DMT, which occurred much earlier than discontinuation. The most commonly documented reasons for non-persistency were perceived lack of efficacy, adverse events, and fear of
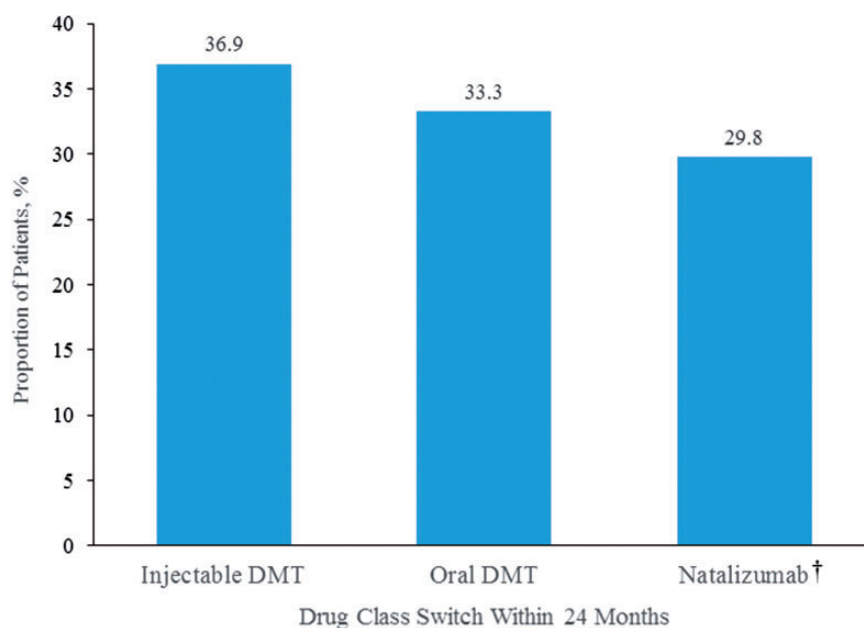

Figure 3. Proportion of patients who switched from iDMT ($n = 84$) by DMT drug class to which they switched. [†]There were no switches to infusion DMTs other than natalizumab. DMT: disease-modifying therapy; iDMT: injectable disease-modifying therapy.
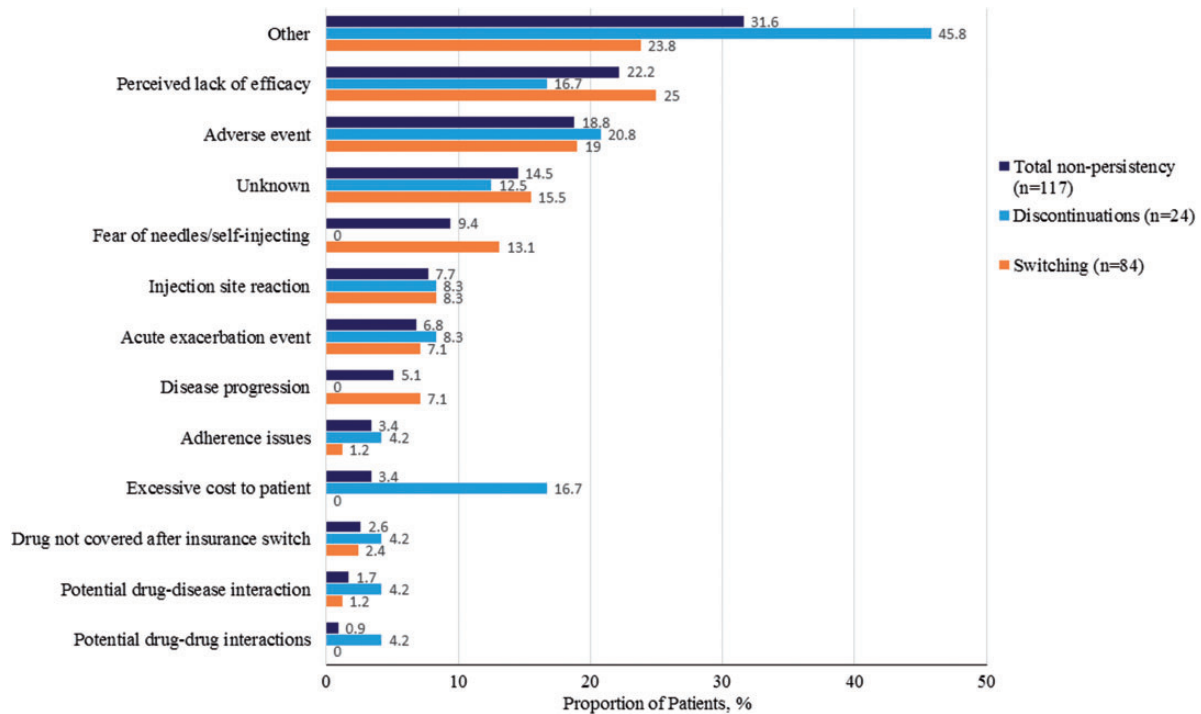
Figure 4. Reasons for injectable disease-modifying therapy total non-persistency, switching, and discontinuations among patients with these treatment changes over 24 months.
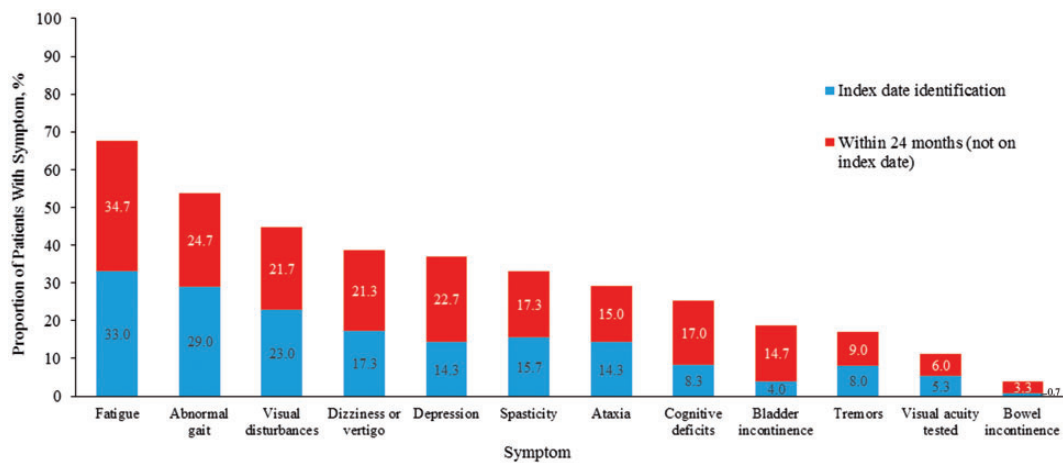

Figure 5. Incidence of symptoms at index date and within 24 months in patients who did not have symptoms at index.

needles/self-injecting. Although 61% of patients were persistent with their index treatment, in the overall study population, relapses, MRI disease progression, and incidence of MS-related symptoms all increased by the end of 24 months.

Non-persistency in the form of switching or discontinuation can have a notable negative impact on RRMS. Patients who switch may have a lapse between treatments and it can take several months

for a DMT to reach full effectiveness,[25] during which time disease may become more active. Lack of persistency to DMTs has been shown to significantly increase the likelihood of hospitalizations and emergency room visits.[26] Furthermore, patients who are non-adherent to DMTs have a higher risk of relapse.[27,28]

In some patients, influenza-like symptoms associated with the IFN DMTs and injection-related tolerability

issues may be barriers to persistency with iDMTs.[9] In this study, adverse events and fear of needles/self-injecting were among the most common reasons for switching or discontinuing treatment. Oral DMTs may be a suitable treatment option for patients who are non-persistent to iDMT because of injection-related adverse events. However, clinicians and patients must weigh the respective benefit/risk profiles of oral DMTs when making treatment decisions. The timeline of this study was mainly after the introduction of the first oral DMT (fingolimod, 2010), which may have affected patient expectations regarding iDMT tolerability and physician prescribing. Other than the current study, few studies have investigated the persistency of iDMT since the introduction of oral DMTs. Warrender-Sparkes et al.[24] conducted an international, observational cohort study of patients in the MSBase registry to assess the effect of the introduction of fingolimod on iDMT persistency. The study found that the likelihood of discontinuation increased significantly after fingolimod became available (hazard ratio = 1.64, $p < 0.001$ vs pre-fingolimod). The study also found that, consistent with the current analysis, persistency was approximately 80% one year after iDMT initiation, which decreased to 65% by year 2. In a retrospective cohort pharmacy claims study designed to compare compliance between fingolimod and iDMT, persistence with iDMT after one year was somewhat lower than in the current study, at approximately 50%. Another retrospective US claims database designed to compare the persistency of fingolimod with iDMT determined that the persistency of iDMTs was approximately 58% after one year.[11] Based on ''real-world'' observational studies or retrospective database analyses, the two-year persistence of iDMT before the availability of oral DMTs ranged from 32% to 92%.[12–14,17,20,22] Given the broad range of reported persistency with iDMT in the pre-oral DMT era, it is difficult to make any conclusions based on the current study regarding any change in the persistence rate since the introduction of oral DMTs. However, the data in this study indicate that persistence with iDMTs remains an issue.

In the current study, approximately one-third of the patients switched to an oral DMT, whereas 37% switched to another iDMT and 30% switched to natalizumab. These results are similar to those found by Warrender-Sparkes et al.,[24] wherein 42% of patients switched to fingolimod and 37% switched to another iDMT. Many factors need to be considered when switching DMTs, including comorbidities, convenience, pregnancy, ability to comply with treatment, tolerability, and disease severity. In addition, because of formulary and insurance mandates, a step-wise approach to therapy may be required, with evidence of ''failure'' of an iDMT needed before a switch to an oral DMT or natalizumab will be covered.

Research indicates that pathologic damage occurs early in the course of RRMS, and early treatment reduces disease progression.[29–33] As such, it seems prudent to consider a switch to a more efficacious treatment if patients are not responding well to initial treatment.[34] The observed increases in the relapse rate and MRI changes in the current study may be indicators of natural disease progression, and may account for the 30% of patients who switched to natalizumab. Natalizumab has been shown to be more effective than iDMTs in patients with more active disease who switched from an iDMT,[35] and may therefore be more often prescribed to these patients. In addition to natural disease progression, it is possible that the increases in the relapse rate and MRI changes could be reflective of the observed iDMT non-persistency. In the subgroup comparison of non-persistent vs persistent patients, the non-persistent patients had higher relapse rate, more symptoms, and more MRI disease progression. However, the study was not designed or powered to evaluate a comparison between non-persistent and persistent patients and the results should be interpreted with caution. The study could not determine if persistency led to better outcomes, or if non-persistent patients had more severe disease and thus discontinued their initial iDMT.

This study was subject to a number of limitations, many of which are related to the retrospective chart review study design. For example, there was a potential bias in the recording of observations since a number of different abstractors collected the information. However, an abstraction manual was developed and used for training, after which an inter-rater reliability assessment was completed by each abstractor in order to reduce this bias. The medical records may have been missing data as clinician input can be variable and pharmacy claims were not confirmed for refills, switches, restarts, or discontinuations. Thus, without actual prescription fill data for verification, persistency may have been over-reported. The neurology practices and medical records were not randomly selected and may not be representative of national prescription and neurology practice patterns. Finally, the sample size was small and under-represented the Western region of the US. Subsequently, there was low power for more robust

comparative analyses of the iDMT cohorts identified and followed in this study.

Conclusions

Over 24 months, 39% of patients were non-persistent on their initial iDMT, indicating that persistency of iDMTs in the age of oral DMTs remains an issue. Among the 61% of patients who remained persistent after 24 months, many still experienced relapses, MRI disease progression, and MS-related symptoms. The fairly high rate of disease progression as evidenced by reported relapses and changes in adverse MRI findings, combined with a higher MS-related symptom burden and low persistency rate for iDMT, suggests that treatment with DMTs that are more efficacious should be considered in some patients. More efficacious treatments with a higher persistency rate may have more profound effects on prevention of disease progression, and therefore, decrease MS-related symptom burden. A greater understanding of reasons for non-persistency such as treatment-related tolerability, adverse events, and effectiveness of iDMT agents at distinct time points may also inform appropriate treatment selection and management.

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