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Medication adherence/persistence among patients with active multiple sclerosis in Finland

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Objectives: To explore adherence, persistence, and treatment patterns in patients with multiple sclerosis (MS) in Finland treated with disease-modifying therapies (DMTs) for active MS in 2005-2018.

Materials and Methods: The study cohort was identified using the Drug Prescription Register of Social Insurance Institute, Finland. All patients had at least one prescription of glatiramer acetate (GA), beta-interferons, teriflunomide, or delayed-release dimethyl fumarate (DMF). Adherence was calculated using proportion of days covered (PDC) (cutoff ≥0.8). Time to non-persistence was calculated by the number of days on index DMT treatment before the first treatment gap (≥90 days) or switch and analyzed with time-to-event methodology.

Results: The cohort included 7474 MS patients (72.2% female; mean age 38.9 years). Treatment switches were steady over 2005-2012, peaked in 2015. PDC means (standard deviations) were GA, 0.87 (0.17); beta-interferons, 0.88 (0.15); DMF, 0.89 (0.14); teriflunomide, 0.93 (0.10). Adherence frequencies were GA, 78.4%; beta-interferons, 81.3%; DMF, 86.9%; teriflunomide, 91.7%. Logistic regression showed that age group, DMT and the starting year, sex, and hospital district independently affected adherence. Patients receiving teriflunomide and DMF, males, and older patients were more likely to persist on treatment. There was no difference in persistence between patients prescribed teriflunomide and DMF, or between GA and beta-interferons.

Conclusions: Oral DMTs had greater adherence and persistence than injectable DMTs.

KEYWORDS

adherence, medication, medication non-adherence, medication persistence, multiple sclerosis, relapsing-remitting

1 | INTRODUCTION

Poor treatment adherence is associated with increased relapse frequency, greater healthcare resource utilization, increased cost, and poorer patient outcomes than observed in adherent patients.[1-3] Therefore, it is vital to identify the frequency and understand the reasons for non-adherence in patients with multiple sclerosis (MS).

From the 1990s to 2011, beta-interferons and glatiramer acetate were standard first-line disease-modifying therapies (DMTs) for

active relapsing-remitting MS (RRMS).[4,5] When started early in the disease course and administered regularly, these injectable agents offer reduced numbers of clinical relapses and prevention of new lesion formation visualized on MRI.[1] During the past decade, several DMTs for active RRMS, including the oral agents delayed-release dimethyl fumarate (DMF), fingolimod, and teriflunomide, have become available.[4] Although the expansion in treatment options for RRMS is welcomed, healthcare professionals are now faced with complicated decisions on how to individualize therapy for patients.[6]

Treatment adherence refers to the extent to which a patient's behavior coincides with a treatment plan, whereas persistence is the duration over which a patient continues with therapy.[7] Several factors affect MS medication adherence and persistence, and these may vary over the course of the disease.[7] For instance, it is reported that among patients with MS treated with beta-interferons or glatiramer acetate, most discontinuations occur in the first 2 years of therapy, and lack of efficacy (30%-50%) and adverse events (22%-70%) are the most common reasons for treatment termination.[7]

A systematic review of 24 studies investigating adherence to injectable DMTs (beta-interferons or glatiramer acetate) reported adherence rates ranging from 41% to 88% in patients with MS.[2] Reasons identified as potential barriers to adherence to injectable DMTs included forgetting to inject, patient-perceived lack of efficacy, injection anxiety, and adverse effects, including injection site reactions, flu-like symptoms, and fatigue.[2] A recent retrospective claims analysis performed in Canada reported higher compliance (defined as medication possession ratio ≥80%) at 6, 12, and 24 months following treatment initiation with the oral agents DMF (70%, 68%, and 56%, respectively), teriflunomide (76%, 76%, and 68%, respectively), or fingolimod (75%, 75%, and 70%, respectively), compared with beta-interferons or glatiramer acetate (53%, 47%, and 35%, respectively).[8] A number of other studies have reported varying degrees of non-adherence in patients with MS, with multiple factors identified as influencing factors, including patient age, sex, MS history, comorbidities, socioeconomic status, and route of treatment administration.[9-14]

In Finland, an estimated 10 000-11 000 individuals have MS.[15] The impact of the introduction of oral DMTs on treatment adherence and persistence is not known in Finland. The present study will utilize nationwide population-based data from the Drug Prescription Register of the Social Insurance Institute in Finland to describe baseline characteristics of patients with MS in Finland treated with DMTs for active RRMS and explore adherence, persistence, and treatment patterns among these patients.

2 | MATERIALS AND METHODS

2.1 | Study population

The study cohort included patients with a diagnosis of MS (International Classification of Diseases [ICD], 10th Revision code G359; ICD, 9th Revision code 340; or ICD, 8th Revision code 340.99) in the Drug Prescription Register of the Social Insurance Institute, a Finnish registry covering the total population in 20 of 21 hospital districts and 100% of drugs prescribed for MS in Finland from January 2005. Of these, we identified those with active RRMS, defined as having at least one prescription of a DMT from January 2005 to December 2018, including glatiramer acetate, beta-interferons, teriflunomide, or DMF. The definition for active MS was based on the criteria for reimbursement of DMTs for active MS, which includes an Expanded Disability Status Scale score < 6.5 and, during the preceding two years, either 2 symptomatic relapses or 1 symptomatic relapse and one separate MS lesion on MRI. While fingolimod was available during the study period, it is used for the treatment of highly active MS and our analyses included only DMTs used for treatment of active MS. If fingolimod had been included, other DMTs such as natalizumab and alemtuzumab, used during the time period 2005-2018 for treatment of highly active MS, would also have needed to be included in the analyses. All intravenously administered DMTs are hospital products in Finland and are not included in the Drug Prescription Register of the Social Insurance Institute; therefore, they were not included in these analyses. Patients were identified retrospectively. The index date was the date of the first DMT purchase.

2.2 | Outcome measures

2.2.1 | Baseline demographics

Demographic characteristics collected for each patient included age on index date, sex, calendar year of index, and treatment history (treatment naive or switch).

2.2.2 | Adherence

Adherence was measured using the proportion of days covered (PDC), defined as the number of doses dispensed in relation to the dispensing period (or length of clinical benefit based on the label for medical claims) during the post-index period, in relation to the number of days between the index date and the last available day of the index DMT during follow-up:

PDC is defined as the total number of days supplied for all prescription fills divided by the number of days between the first and last prescription fill plus number of days' supply of the last fill.

2.2.3 | Persistence

The time to non-persistence was calculated by the number of days a patient was on the index DMT until the start of the first treatment gap (≥90 days) or the switch of treatment.

2.3 | Statistical methods

Summary statistics for baseline demographics were calculated as means, medians, and standard deviations (SDs) (continuous measures), or frequency and percent (categorical measures). Variables

found to be associated with adherence or persistence following univariate analysis were included in multivariate models for both adherence and persistence.

Adherence was calculated using a PDC cutoff value of ≥0.8. Logistic regression was used to evaluate the differences in the proportion of patients who adhered to their index DMT between the groups (age group, sex, DMT cohort, index year, hospital district). The pairwise differences of the groups were quantified with odds ratios and their 95% confidence intervals.

Persistence was analyzed by applying time-to-event methodology using the Kaplan-Meier approach, together with the log-rank test and Cox proportional hazard model. The failure event was defined as non-persistence at any time. In case no such events were detected, the patient and treatment were censored at the time of end of the post-index period. The pairwise differences of the groups (age group, sex, and DMT cohort) were quantified with hazard ratios and their 95% confidence intervals.

All statistical tests tested a two-sided hypothesis of no difference between groups, at a *P*-value level of .05. Data were analyzed using SAS/STAT software, version 9.4, of the SAS System for Windows (SAS Institute).

3 | RESULTS

3.1 | Patient characteristics

Baseline demographics are summarized in Table 1. A total of 7474 patients with MS were included in the cohort, of which 5398 (72.2%) were female. Mean (SD) age at index date was 38.9 (10.6) years, and the majority of patients (n = 5134; 68.7%) were aged ≤44 years at index date.

TABLE 1 Baseline characteristics

Baseline characteristics	N = 7474
Female, n (%)[a]	5398 (72.2)
Mean (SD) age at index date, years[a,b,c]	38.9 (10.6)
Age at index date, y, n (%)[a,b,c]	
18-34	2695 (36.1)
35-44	2439 (32.6)
45-54	1658 (22.2)
55-64	575 (7.7)
≥65	45 (0.6)

Abbreviation: SD, standard deviation.

[a]Five (0.1%) patients were missing data.

[b]The index date was the date of first disease-modifying therapy purchase.

[c] Patients aged <18 years (n = 57 [0.8%]) were excluded from all analyses.

3.2 | Patterns of DMTs

From 2005 to 2013, two types of DMTs were recorded: beta-interferons and glatiramer acetate. During this time period, the number of patients initiating a DMT ranged from a total of 518 in 2006 to 665 patients in 2008; approximately one-third of patients initiating a DMT were prescribed glatiramer acetate (range over the time period, 29.8%-41.3%), and two-thirds of patients were prescribed beta-interferons (range over the time period, 58.7%-70.2%). Use of teriflunomide began in 2014 (n = 132; 22.6%) and DMF in 2015 (n = 468; 42.4%). There was a noticeable increase in the total number of patients initiating or switching a DMT in 2015 (n = 1104) and 2016 (n = 1118) compared with previous years. In 2018, glatiramer acetate was initiated by 86 (13.5%) patients, beta-interferons by 83 (13.1%) patients, teriflunomide by 185 (29.1%) patients, and DMF by 281 (44.3%) patients.

Duration of DMTs use by individual hospital districts is shown in Figure S1 (Supporting Information). Across hospital districts, the majority of patients (50.0%-65.1%) used DMTs for >2 years through the study period. However, the number of patients receiving DMTs in districts 22 and 25 was small (31 and 6, respectively). Generally, the majority of patients (~52%-100%) used glatiramer acetate and beta-interferons for >2 years. In districts where teriflunomide or DMF was used by ≥30 patients, the majority were treated for >1 year.

The number of treatment switches increased steadily from 2005 (n = 108; 2.0%) to 2012 (n = 259; 4.8%), peaked in 2015 (n = 877; 16.4%), and then declined in 2018 (n = 431; 8.1%) (Figure 1).

3.3 | Treatment adherence

Between 2005 and 2012, the proportion of patients who were adherent to their DMT ranged from 77.2% to 80.3%; thereafter, the proportion increased, reaching almost 90%. Mean (SD) PDC was >0.8 for all four DMT cohorts: teriflunomide, 0.93 (0.10); DMF, 0.89 (0.14); beta-interferons, 0.88 (0.15); and glatiramer acetate, 0.87 (0.17) (Figure 2). The proportions of patients who were adherent to treatment (defined as PDC ≥0.8) were 91.7% for teriflunomide, 86.9% for DMF, 81.3% for beta-interferons, and 78.4% for glatiramer acetate (Figure 2). In the logistic regression analysis, age group, DMT, index year, sex, and hospital district each had an independent effect on adherence with univariate analysis; these effects were retained when analyzed by multivariate analysis (Table 2). Exploratory univariate analysis by DMT cohort also showed that hospital district had an effect on adherence in the glatiramer acetate and beta-interferon cohorts but not within the teriflunomide and DMF cohorts (Table 2). Pairwise comparisons of treatments showed a statistically significant difference in adherence between all treatments in a univariate analysis (Table 3).

3.4 | Treatment persistence

Patients receiving teriflunomide or DMF were more likely to persist with treatment than those receiving glatiramer acetate or

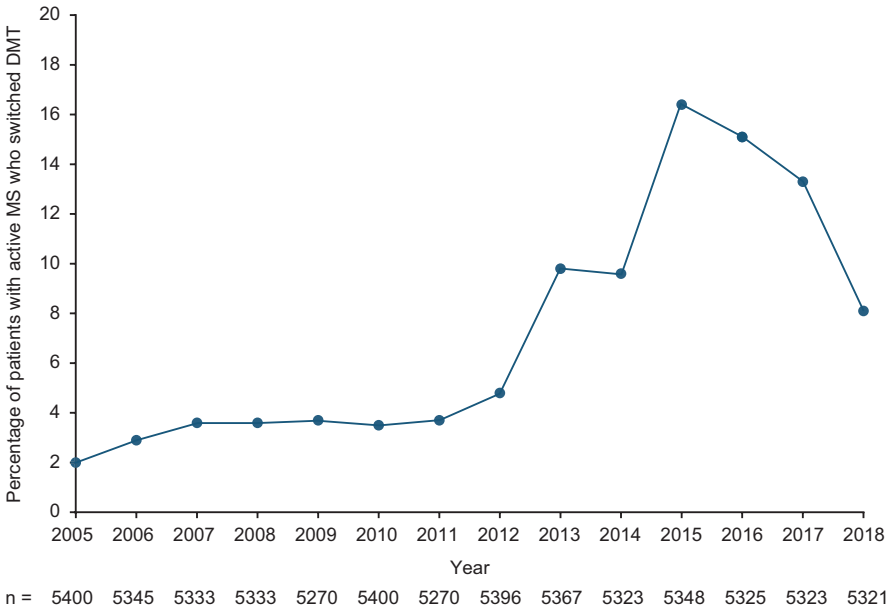

FIGURE 1 Proportion of patients who switched disease-modifying therapies (DMT) for active relapsing-remitting multiple sclerosis by year of switch. All beta-interferons were considered to be one treatment. DMT included delayed-release dimethyl fumarate, glatiramer acetate, beta-interferons, and teriflunomide

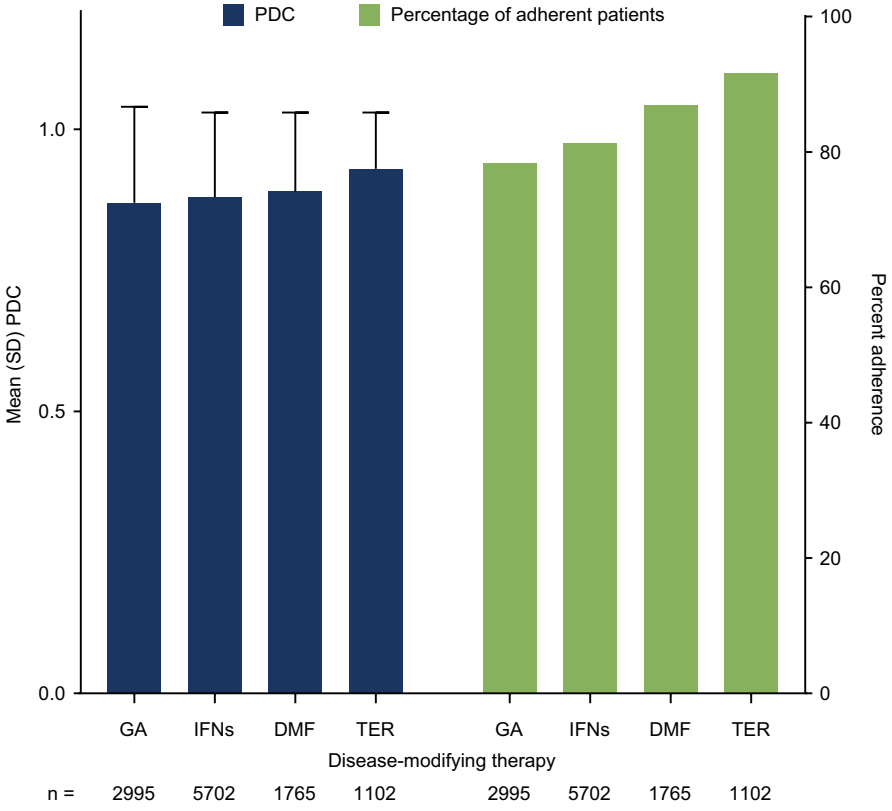

FIGURE 2 Mean proportion of days covered (PDC) and adherence (PDC cutoff ≥ 0.8). Error bars for mean PDC represent standard deviation (SD). Abbreviations: DMF, delayed-release dimethyl fumarate; GA, glatiramer acetate; IFN, beta-interferon; TER, teriflunomide

beta-interferons; there was no difference in persistence between patients taking teriflunomide and DMF or between patients taking glatiramer acetate and beta-interferons (Figure 3A). Male patients were more likely to persist with treatment than female patients (log-rank test for overall difference between sexes, $P < .0001$) (Figure 3B). Analysis by age group showed a decrease in treatment persistence with younger age grouping (log-rank test for overall difference between age groups, $P < .0001$) (Figure 3C). Time to non-persistence was not statistically significantly different across hospital districts for all DMTs, except for beta-interferons (log-rank $P = .0008$; Table S1; Supporting Information).

4 | DISCUSSION

This retrospective population-based study is the first to investigate treatment patterns and treatment adherence and persistence among patients initiating DMTs for active RRMS in Finland. Prior

TABLE 2 Logistic regression analysis for adherence

Variable	Univariate analysis *P*-value	Multivariate analysis[b] OR	95% CI	*P*-value
Age, y	<.0001			<.0001
18-34 vs ≥55		0.275	0.216-0.351	
35-44 vs ≥55		0.510	0.399-0.653	
45-54 vs ≥55		0.753	0.580-0.977	
Sex	.0048	1.160	1.034-1.300	.0112
Hospital district	<.0001			<.0001
Within teriflunomide	.6876			NA
Within glatiramer acetate	.0090			NA
Within beta-interferons	.0019			NA
Within delayed-release dimethyl fumarate	.1958			NA
Index year[a]	<.0001			<.0001
DMT	<.0001			<.0001
Glatiramer acetate vs delayed-release dimethyl fumarate		0.830	0.658-1.048	
Teriflunomide vs delayed-release dimethyl fumarate		1.576	1.213-2.049	
Beta-interferons vs delayed-release dimethyl fumarate		1.114	0.879-1.411	

Abbreviations: CI, confidence interval; DMT, disease-modifying therapy; NA, not available; OR, odds ratio.

[a]First record of DMT prescription.

[b]Included effects with $P < .05$ in the univariate analysis.

TABLE 3 Univariate logistic regression analysis for differences in adherence between disease-modifying therapies

Therapy comparison	Odds ratio	95% confidence interval	*P*-value
Teriflunomide vs glatiramer acetate	3.033	2.409-3.819	<.0001
Teriflunomide vs beta-interferons	2.532	2.024-3.166	<.0001
Teriflunomide vs delayed-release dimethyl fumarate	1.660	1.287-2.141	<.0001
Glatiramer acetate vs beta-interferons	0.835	0.748-0.931	.0012
Glatiramer acetate vs delayed-release dimethyl fumarate	0.547	0.465-0.645	<.0001
Beta-interferons vs delayed-release dimethyl fumarate	0.656	0.562-0.765	<.0001

to 2014, the number of patients initiating a DMT ranged from 518 to 665 per year. There were marked increases in the numbers of patients initiating a DMT following the introduction of teriflunomide in 2014 and DMF in 2015, with patient numbers almost doubling in 2015 (n = 1104) and 2016 (n = 1118), respectively. By 2018, almost three-quarters (73.4%) of patients initiating a DMT started treatment with one of the new oral agents rather than an injectable agent. In addition, a rapid increase in the number of treatment switches was recorded from 2013 to 2015, also corresponding with the timeframe of oral DMT introduction. This suggests possible patient preference for oral versus injectable agents for MS therapy initiation, which would agree with outcomes from a web-based conjoint analysis survey performed in the USA; this reported a preference for oral daily medications versus biweekly subcutaneous or once-weekly intramuscular injections.[16]

Adherence to DMTs in patients with MS reported in the literature is highly variable, possibly reflecting the high variability in study design and outcome measures.[12] Although study designs vary, the adherence rates reported here for oral DMTs are comparable with those reported by Johnson et al, Duquette et al, and Setayeshgar et al and are relatively high compared with other studies.[3,8,10,11,14] In the current study, the proportions of patients adherent to treatment were higher for the two oral agents (2544/2867; 88.7%) than for the injectable agents (6982/8697; 80.3%). Also, patients on teriflunomide showed better adherence than patients using DMF, which may be due to difference in dosing scheme (teriflunomide once daily vs. DMF twice daily). In other therapeutic areas, higher dosing frequency has been associated with lower adherence in several,[17-20] but not in all, [21,22] studies. In addition, persistence to treatment was also higher with oral agents versus injectables. Previous claims-based studies have reported mixed outcomes regarding adherence and persistence for oral and injectable DMTs in patients with MS.[3,8,13,14] In the study by Higuera et al, the probability of adherence to self-injectable agents was dependent upon the side effect profile of the

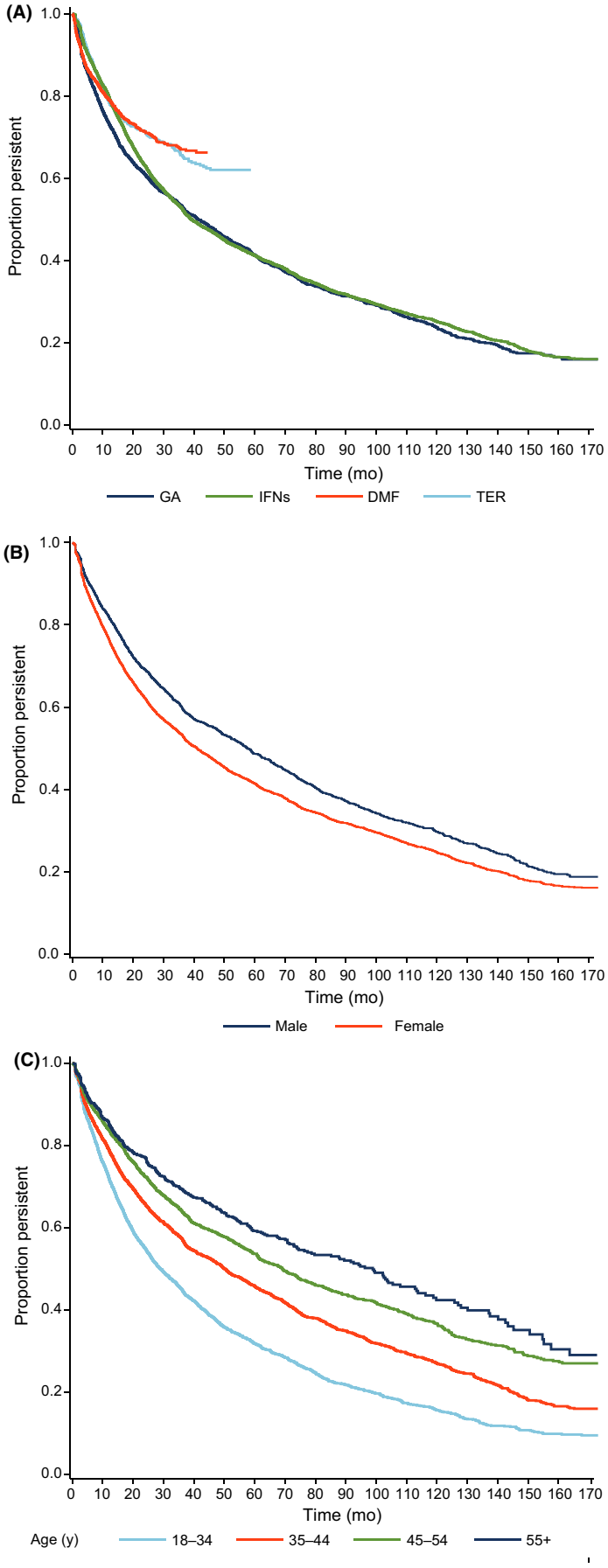

FIGURE 3 Time to non-persistence to treatment including switch by A, disease-modifying therapy, B, sex, and C, age. Abbreviations: DMF, delayed-release dimethyl fumarate; GA, glatiramer acetate; IFN, beta-interferons; TER, teriflunomide

agent; lower adherence was reported for agents with injection site reactions classified as the most likely side effect than for oral, infusible, or self-injectable DMTs.[13]

Consistent with previous studies, male sex and older age were associated with improved adherence and persistence to treatment in this study.[9,13,14] Given that MS is more prevalent in females than in males, lower rates of adherence in female patients likely have a great impact in this patient population and highlight an area for further investigation. It is also possible that lower persistence in young females could be related to pregnancy-related treatment gaps. The impact of age on treatment adherence in patients with MS is not fully understood.

Shared decision-making between patients and healthcare professionals may have a positive effect on adherence to DMT and patient satisfaction with MS care.[23,24] Behavioral, clinical, social, and financial aspects should be considered when choosing the DMT, and both patient and clinician should have a good understanding of available treatments.[23] Special attention should be paid to active communication between the patient and clinician, as well as to patient preferences (eg, route of administration, tolerance, lifestyle, and work environment), education, and engagement, as these are important components of shared decision-making.[23] Importantly, the majority of patients with MS prefer to have an active role in medical decision-making,[25] and shared decision-making has not been shown to increase anxiety among patients with MS.[26] In Finland, shared decision-making is advocated in all hospital districts, but the level of patients´ participation may vary individually and between districts.

4.1 | Limitations of the research methods

There were a small number of events in some subgroups. Also, the dataset did not contain all desirable information for further investigation of confounding factors, such as detailed clinical characteristics (eg, MS severity or disability level), socioeconomic status, frequency of hospitalizations, presence of comorbid conditions, or treatment effectiveness. In addition, the use of PDC to evaluate adherence has been criticized by some researchers as PDC measures the patterns of medication refills rather than actual medication use.[14,27] Also, the treatment naïve vs switch data were not available in our analysis, as the injectable therapies were already in use before 2005 in Finland.

5 | CONCLUSION

In this population-based cohort of patients with MS in Finland, adherence to treatment was better with oral DMTs compared with injectable DMTs. Overall adherence to treatment increased from 2013, which was before oral DMTs for active RRMS became available and might reflect an increase in general awareness of MS disease and the importance of treatment adherence. Given its impact on patient outcomes and healthcare resources, the importance of adherence to DMTs should be discussed as part of patient-centered medical care and shared decision-making.

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CONFLICT OF INTEREST

S. Lahdenperä and A. Berglund are employees of and hold stock/stock options in Biogen. M. Soilu-Hänninen received speaker fees from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva; congress expenses from Biogen, Merck, Roche, Sanofi-Genzyme, and Teva; and served on advisory boards for Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. H. Kuusisto received lecture fees from Biogen, Merck, Novartis, Sanofi-Genzyme, and Teva; congress expenses from Merck, Sanofi-Genzyme, Teva, and Zambon; and served on advisory boards for Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. S. Atula received lecture fees from Merck, Roche, Santen, and Teva; congress expenses from Biogen, Genzyme, Merck, Orion, and Pfizer; and consulting fees from Biogen, Genzyme, Merck, Pfizer, and Roche. J. Junnila declares no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available upon request and detailed at this website (http://clinicalresearch.biogen.com).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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