UNIVERSITA' DEGLI STUDI DI MILANO BICOCCA
CENTRO DI STUDIO E RICERCA
SULLA SANITA' PUBBLICA
Villa Serena - 6° piano, - Via Pergolesi 33, I- 20052 MONZA
E-mail: cesp@unimib.it Tel +39 039 2333097-8

UNIVERSITÀ DI PISA

20 ANNI
ARS TOSCANA
agenzia regionale di sanità

ANALYSIS OF TREATMENT PATTERNS WITH DISEASE MODIFYING THERAPIES (DMTs) AMONG PATIENTS WITH MULTIPLE SCLEROSIS

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2. LIST OF ABBREVIATIONS

ATC	Anatomical therapeutic chemical classification system
CNS	Central nervous system
DDD	defined daily dose
DMT	Disease modifying therapy
FED and SPF	Drug dispensing records
ICD9CM	International Classification of Diseases, Ninth Revision, Clinical Modification
MS	Multiple sclerosis
MRI	Magnetic resonance imaging
PML	Progressive multifocal leukoencephalopathy
SDO	Hospital discharge records
SEA	Disease-specific exemptions from co-payment to health care

3. RESPONSIBLE PARTIES

University of Milan-Bicocca
Prof. Giampiero Mazzaglia
Dr. Ippazio Cosimo Antonazzo
Dr. Carla Fornari

Agenzia di sanità della toscana (ARS)
Dr. Rosa Gini
Dr. Claudia Bartolini
Dr. Giulia Hyeraci

University of Pisa
Dr. Ersilia Lucenteforte
Dr. Silvia Tillati
Dr. Sabrina Giometto

4. ABSTRACT

Title

Analysis of treatment patterns with Disease modifying therapies (DMTs) among patients with multiple sclerosis

Background and rationale

Multiple Sclerosis (MS) is a neurodegenerative disease characterized by chronic inflammation of the central nervous system that affects young adults. The most diagnosed type of MS is represented by the Relapse Remitting MS (RRMS) that accounts for almost 85% of cases. Generally, RRMS is characterized by periodic relapse, with exacerbation of existing symptoms or new one, followed by partial or complete recovery (remitting phase). Although the complete pathogenesis is still far to be completely elucidated, both T- and B- immune cells play a crucial role in disease onset and worsening representing the target for MS disease modifying therapies (DMTs). In the last decades, several new drugs have been approved as treatment for RRMS. The availability of new drugs enables physicians in choosing treatment according with patients and disease characteristics.

To the best of our knowledge, few studies have investigated treatment patterns of DMTs. These were mainly focused on treatments adherence/persistence, and their associated determinants, based on pairwise comparison between old treatment options with a relatively short follow-up and censoring after the first studied event (i.e., switch from the initial treatment). The increased availability of new DMTs calls for new drug-utilization studies able to explore the patterns of DMTs in real-life setting over a longer follow-up.

Objectives

To describe treatment use, patterns, and related determinants of DMTs dispensed in patients with MS over a 12-year period. Specific objectives are as follows:

- To estimate the population-based yearly prevalence, incidence, and consumption of DMTs;
- To describe demographic and clinical characteristics of patients with MS newly treated with DMTs;
- To estimate the incidence of switches, interruptions and drug discontinuations (i.e., number, time to events, type of second- third-line treatments) among patients with MS newly treated with DMTs;
- To estimate the impact of demographic and clinical characteristics on the relationship between DMTs specific exposure and treatment patterns (i.e., switches, interruptions, and drug discontinuations)

Study design and data source

This will be a retrospective cohort study based on healthcare administrative database (HAD) of Tuscany. The HAD collects pseudo-anonymized patient-level information on the utilization of healthcare services reimbursed by the National Healthcare Service and dispensed to all subjects living in the relevant catchment areas. For each subject information will be retrieved by using the following databases: demographic registry, hospital records, outpatient care records, dispensing pharmacy claim records, database of diseases - specific exemptions codes from co-payment to health care, and pregnancy registry.

Study population

To estimate population-based yearly prevalence, incidence, and consumption of DMTs use, subjects with at least one dispensing of a MS treatment between January 1st, 2010, and December 31st, 2021 will be considered.

To investigate treatment patterns with MS newly treated with DMTs will be selected. The first ever dispensation of any DMTs for MS within January 1st, 2010, and December 31st, 2016 defines the new users, the date of first ever DMTs supply will be the "*index date*" and the corresponding drug will be the "*index drug*".

The following inclusion criteria will be applied:

- All individuals aged ≥18 years
- Actively registered in the demographic registry 3 years prior to the index date

Follow-up period will be defined as interval between the index date until the occurrence of the following events (i.e., "*end of follow-up*"): disenrollment from the healthcare plan, censoring events (i.e., death, pregnancy, and malignancy), or the end of the study period (31st December 2021), whichever comes first.

Variables of interest

Drug utilization section

- *Prevalent users*: subjects with at least one dispensation of any DMTs during each study year
- *Incident users*: subjects with at least one dispensation of any DMTs during each study year and no DMTs use in the year before
- *DMTs consumption*: calculated among prevalent users by dividing the total amount of Defined Daily Dose (DDD) dispensed with the estimated number of prevalent users.

Treatment patterns section

Consecutive DMTs dispensing will be firstly converted into *treatment episodes,* defined as a series of uninterrupted dispensing with the same DMT. Patients may have one or multiple treatment episodes during the study period. Accordingly, they will be classified according to the following mutually exclusive treatment patterns:

- *Continuers*: patients with a single treatment episode covering the entire follow-up period.
- *Discontinuers:* patients with a single treatment episode not covering the entire follow-up period.
- *Interrupters:* patients with two or more treatment episodes of the index drug covering or not covering the entire follow-up period.
- *Switchers:* patients having one or more new DMTs during or after the previous treatment episode with the index (or another) drug, covering or not covering the entire follow-up period.
- *Mixed users:* patients having a combination of interruptions and switches, covering or not covering the entire follow-up period.

Statistical analysis

- Incidence, prevalence, and consumption of DMTs use will be estimated yearly during the study period.
- Subjects will be grouped according to the first DMT dispensed in the study period. Then, each subject will be defined according to their treatment patterns observed during the follow-up. Finally, demographic, and clinical characteristics at the index date, as well as treatment patterns observed during the follow-up, will be summarized through standard descriptive statistic for each drug group.
- For each DMT new user, treatment patterns during the entire follow-up will be plotted by using the Sankey diagram.
- Recurrent events models and time-varying variables will be used to estimate the impact of the demographic and clinical covariates on the relationship between DMTs specific exposure and study outcomes (discontinuation and switch/interruption). Results will be expressed as Hazard Ratio (HR) with 95% CI.

5. BACKGROUND

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease that affects over 2 million people worldwide, corresponding to a prevalence of 30.1 cases per 100,000 individuals (GBD, 2017). The disease distributions vary among different geographic areas, and several factors such as age, gender and latitude may influence its prevalence. Among younger people the prevalence of disease is similar in boys and girls, whereas in adults, the ratio is 2:1 higher in women.

Although the pathophysiological mechanisms are still far to be completely elucidated, the different clinical characteristics are well defined: relapsing-remitting-MS (RRMS), secondary progressive (SPMS), primary progressive (PPMS) and progressive-relapsing (PRMS) (Lublin, 2014). The most diagnosed type of MS is represented by the RRMS that accounts for almost 85% of cases. Generally, RRMS is characterized by periodic relapse, with exacerbation of existing symptoms or new one, followed by partial or complete recovery (remitting phase). In the last phase of the disease, the RRMS can evolve in a more severe form, the SPSM that is characterized by increased accumulation of damage without any recovery. Similar features can be observed in the PPMS that is characterized by damages without recovery since the early phases of the disease (Lublin, 2014).

MS results from complex inflammatory processes that involve both the immune and central nervous systems (CNS). In this intricate pathway, the T- and B-cells play a crucial role (Yadav, 2015). In fact, the deregulation of the immune system alters the functions of the circulating cells with consequent migration from peripheral areas into the CNS (Gonsette, 2012). In the CNS, after the disruption of the blood brain barrier these cells attack the neurons' myelin (Molnarfi, 2013) producing localized areas of damage responsible of clinical manifestation of the disease. The pathologic processes are triggered by several cells and mediators that represent the pharmacodynamic target for the disease modifying therapies (DMTs).

5.1. Rationale

Until a few years ago, the treatment of RRMS with DMTs was rather simple. IFN-β preparations and glatiramer acetate were available as first-line therapy, and if treatment escalation was needed, natalizumab and fingolimod were the only alternatives (Sorensen, 2014). With the availability of more than 15 different therapies acting on different targets

with several mechanisms of actions, today treatment choice is based on patients and disease characteristics (Evans, 2016; Mckay, 2017; Kern 2020). For example, interferon and glatiramer acetate, along with oral drugs like teriflunomide and dimethyl fumarate are generally used as first-line therapies for RRMS, whereas natalizumab, fingolimod, alemtuzumab, ocrelizumab, cladribine, and mitoxantrone are mainly used as second-line therapies in patients who do not respond satisfactorily to a first-line therapy. However, alemtuzumab, like natalizumab and fingolimod, may be also used as first-line therapy in patients with very active RRMS (Ghezzi, 2018).

Very few studies have investigated so far treatment patterns of DMTs (i.e., first and subsequent treatments) in patients with MS over a long follow-up period (Kern 2020). Previous research, in fact, mainly focused on treatments adherence/persistence based on pairwise comparison between interferon and an active control with a relatively short follow-up and censoring after the first switch from the initial treatment (Devonshire 2011; Halpern 2011; Agashivala 2013; Bergvall 2014; Kleinman 2010).

Other studies have also investigated possible determinants for DMTs treatment adherence among patients with MS (Erbay 2018; Higuera 2016; Longbrake 2016; Williams 2018; Agashivala 2013; Bergvall 2014) although they were focused only on older drugs such as interferons (Higuera 2016; Moccia 2020; Bowen, 2020). Therefore, new drug utilization studies are needed to explore the patterns of DMTs in real-life setting.

6. OBJECTIVES

Overall, we wish to describe treatment use, patterns, and related determinants of DMTs dispensed in patients with MS over a 12-year period.

Specific objectives are as follows:

- To estimate the population-based yearly prevalence, incidence, and consumption of DMTs;
- To describe demographic and clinical characteristics of patients with MS newly treated with DMTs;
- To estimate the incidence of switches, interruptions and drug discontinuations (i.e., number, time to events, type of second- third-line treatments) of patients with MS newly treated with DMTs;
- To estimate the impact of demographic and clinical characteristics on the relationship between DMTs specific exposure and treatment patterns (i.e., switches, interruptions, and drug discontinuations).

7. RESEARCH METHODS

7.1. Study design

This study is a retrospective cohort, based on healthcare administrative databanks of Tuscany, and it will be structured in two different sections:

- *Drug utilization section*: population-based descriptive study;
- *Treatment patterns section*: population-based retrospective cohort study of new users of DMTs for MS.

7.2. Setting and data source

This study will use healthcare administrative databanks from Tuscany that account for about 3,729,641 individuals (6% of Italian population).

The Tuscany administrative databanks collect longitudinal pseudo-anonymized patient-level information on the utilization of healthcare services reimbursed by the National Healthcare Service and dispensed to all subjects who are residents and registered with a general practitioner in the relevant catchment areas. For each subject the following databanks will be explored:

- *Demographic databank;* It includes information on age, gender, start and end of registration in the Local Health Authority;
- *Hospital records databank;* It includes information on date of admission and discharge, one main and five secondary diagnoses and 6 procedures coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9CM);
- *Outpatient care databank;* It includes information on information on healthcare services dispensed to free of charge or upon co-payment, such as specialist visits, laboratory or instrumental or bio-imaging diagnostic tests, and procedures in outpatient setting;
- *Dispensing pharmacy claim databank;* It includes information on drugs dispensing (e.g., active principle, ATC code, number of dispensed packages) as well as the date of dispensation. Drugs are registered in two databases: hospital pharmacies and community pharmacies;

- *Diseases databank;* It includes information on exemptions from co-payment to health care;
- *Pregnancy databanks (*certificates of childbirth assistance, CAP, terminations, ABS, and miscarriages databases, IVG)*;* they include information on pregnancy (e.g., childbirth date and interruption date, date of birth).

7.3. Study population

7.3.1. Drug utilization section

We will select patients with the at least one dispensing of DMTs for MS *(see paragraph 7.4.2 and table A1)* living in Tuscany on the 1st of January of each study year (between January 1st, 2010, and December 31st, 2021). We will include all patients with at least 3 year of look back and aged 18+ years. Patients with malignancy in the 3 years prior to the first dispensation will be excluded (see table A2 for details).

7.3.2. Treatment patterns section

- We will identify patients with the first ever dispensation (new users) of any DMTs for MS *(see paragraph 7.4.2 and table A1)* issued between January 1st, 2010, and December 31st, 2016. The date of the first ever DMTs supply will be defined as the "***index date***" and the corresponding drug as the "***index drug***". From the initial cohort, we will only include all patients actively registered in the demographic databank 3 years before, with at least 5 years of follow up after the index date, aged 18+ years, and with no dispensing of DMTs for MS in the period prior the index date. Patients with malignancy in the period prior to index date will be also excluded (see table A2 for details).
- All subjects will be followed-up from the index date until the occurrence of the following events (i.e., "end of follow-up"): *disenrollment from the healthcare plan, censoring events* (i.e., death, pregnancy, and malignancy - see table A2 for details), or the *end of the study period* (31st December 2021), whichever comes first. *The timeframe between the index date and the end of follow-up will be defined as "**follow-up period**".*

7.4. Index drugs

The study will include 13 different drugs (see table Table A1 for details):

- *Injectable therapies*: Glatiramer acetate, Interferon beta-1a, Interferon beta-1b, Peginterferon beta 1a
- *Immunosuppressant*: Dimethyl fumarate, Fingolimod, Teriflunomide, Cladribine, Metothrexate
- *Infusive therapies*: Natalizumab, Alemtuzumab, Mitoxantrone, Ocrelizumab

7.5. Variables of interest

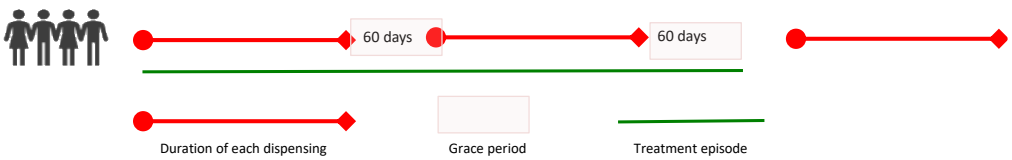
7.5.1. Drug utilization measures

Patients with at least one dispensation of any DMTs during each study year will be considered as ***prevalent users***, whereas those with at least one dispensation of any DMTs during each study year and no DMTs use in the 3-years before will be considered as ***incident users***. ***DMTs consumption*** will calculated among prevalent users by dividing the total amount of Defined Daily Dose (DDD) dispensed with the estimated number of prevalent users.

7.5.2. Treatment patterns

For each selected patient, to identify the associated treatment patterns we will firstly convert consecutive DMTs dispensing into ***treatment episodes,*** defined as a series of uninterrupted dispensing with the same DMT. The duration of each dispensing will be obtained by dividing the total amount of active substance contained in the packages of the dispensed drugs by the corresponding attributed DDD. The treatment episode will be considered uninterrupted if the duration of the gap (grace period) between the end date of dispensing and the subsequent one will be less than 60-days (Figure 1).

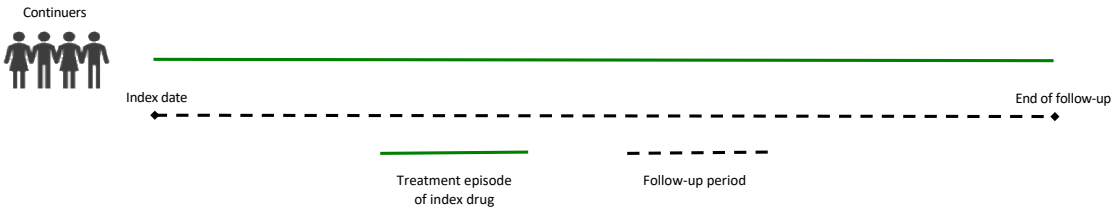
Figure 1. Graphical representation of the treatment episode



Patients may have one or multiple treatment episodes during the study period. Accordingly, they will be classified according to the following mutually exclusive treatment patterns:

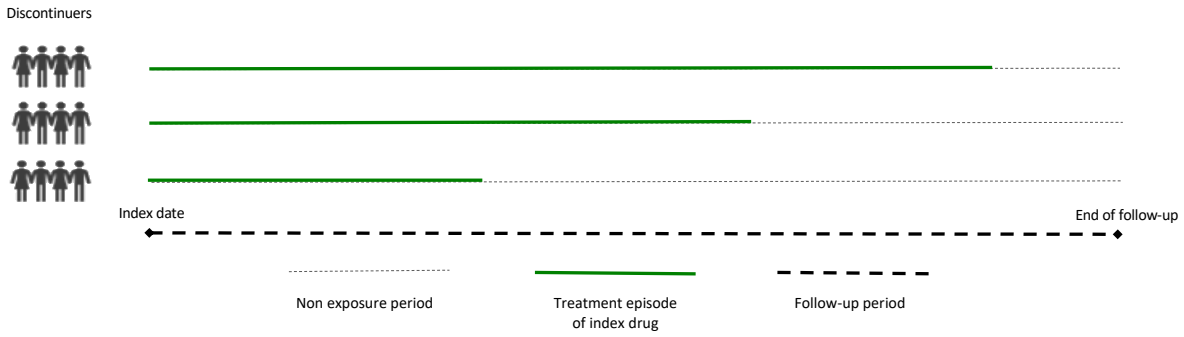
- ***Continuers***: patients with a single treatment episode covering the entire follow-up period (Figure 2).

Figure 2. Graphical representation of continuers



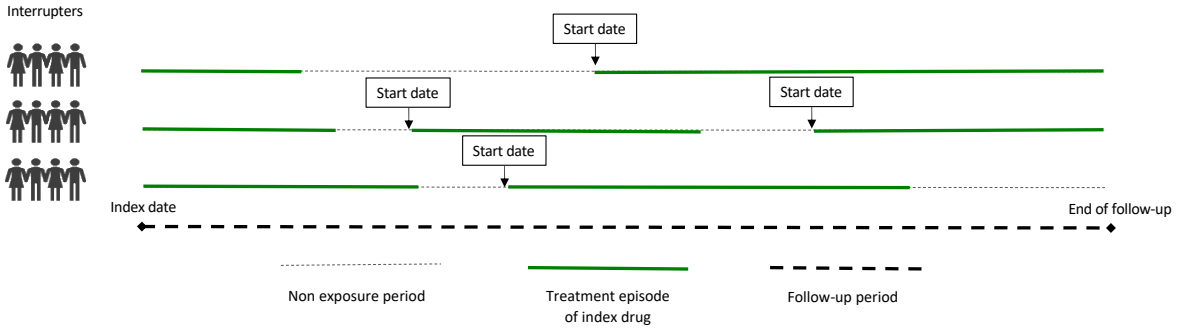
- ***Discontinuers****:* patients with a single treatment episode not covering the entire follow-up period. Therefore, after the end of the first treatment episode no more dispensing will be observed in the remaining follow-up period. In this case, ***time to discontinuation*** corresponds to the duration of the treatment episode and will be considered as the difference (in days) between the end date of the treatment episode and the index date (Figure 3).

Figure 3. Graphical representation of discontinuers



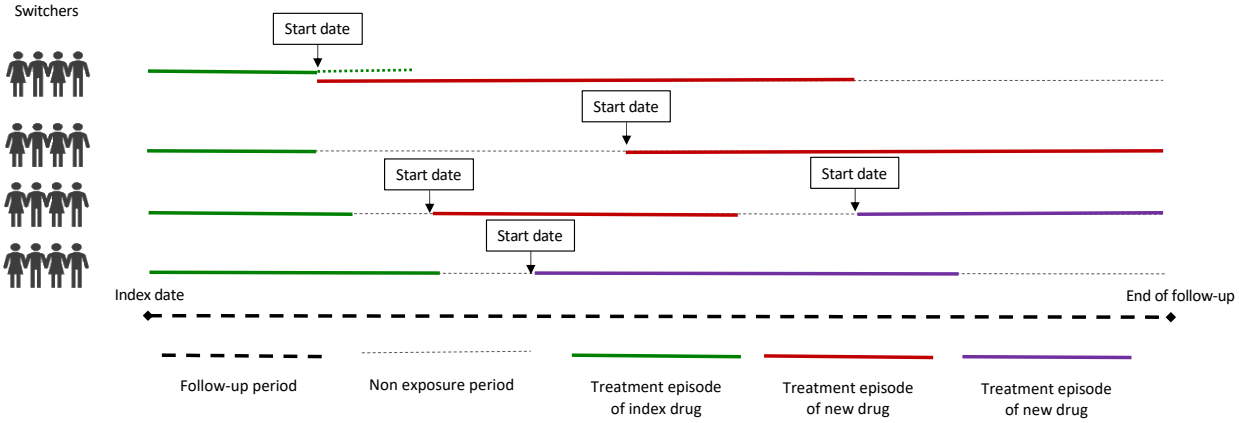
- ***Interrupters****:* patients with two or more treatment episodes of the index drug covering or not covering the entire follow-up period. In this case, ***time to first interruption*** will corresponds to the duration of the first treatment episode and will be considered as the difference (in days) between the end date of the first treatment episode and the index date. Similarly, duration of subsequent treatment episodes will be calculated as the difference (in days) between the end date of the second, third, etc. treatment episode and the ***start date***, defined as the date of start of the corresponding second, third, etc. treatment episode (Figure 4).

Figure 4. Graphical representation of interrupters



- *Switchers:* patients having one or more new DMTs during or after the previous treatment episode with the index (or another) drug, covering or not covering the entire follow-up period. If the dispensing with the new DMT occurs during the previous treatment episode, this indicates the switch, and the previous treatment episode will be cut short at the date of the new dispensing. In this case, ***time to switch*** will be considered as the difference (in days) between the start date of the first switch and the index date. Similarly, in case of additional switches, duration of subsequent treatment episodes will be calculated as the difference (in days) between the end date of the second, third, etc. treatment episode and the *start date*, defined as the date of start of the corresponding second, third, etc. treatment episode (Figure 5).

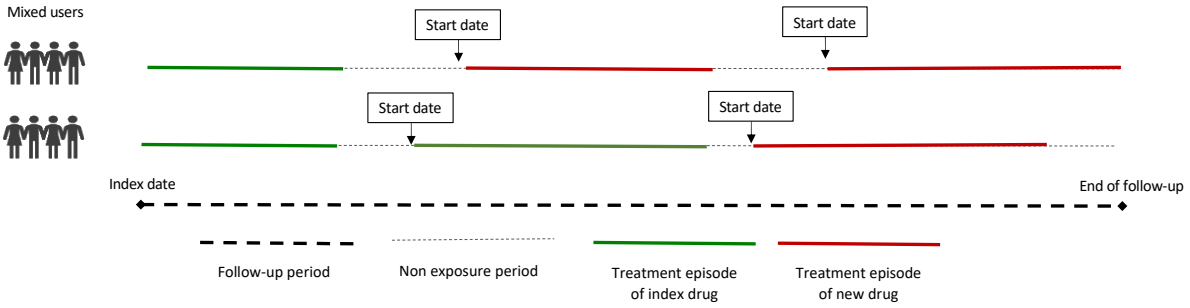
Figure 5. Graphical representation of switchers



- *Mixed users:* patients having a combination of interruptions and switches, covering or not covering the entire follow-up period. In this case, ***time to interruption or switch*** will be considered as the difference (in days) between the start date of the first interruption or switch and the index date. Similarly, in case of additional

interruption or switches, duration of subsequent treatment episodes will be calculated as the difference (in days) between the end date of the second, third, etc. treatment episode and the ***start date***, defined as the date of start of the corresponding second, third, etc. treatment episode (Figure 6).

Figure 6. Graphical representation of mixed users



7.6. Covariates

The following variables will be collected at the index date and during follow-up at the start date:

- Demographic information (i.e., age, sex):
- Clinical information and healthcare services information
  - Comorbidities (Marrie 2012; Marrie 2013a; Marrie 2013b; Marrie 2013c; Marrie Marrie 2015; Edwards 2018 ; Al-Sakran 2020; Magyari 2020; Colais 2021): Hypertension; Diabetes; Dyslipidemia; Mood and anxiety disorders; Chronic lung disease; Epilepsy; Migraine; Ischemic heart disease; Renal disease; Chronic diseases of liver; pancreas and intestine; Autoimmune diseases (Chronic lymphocytic thyroiditis; Inflammatory bowel disease; Ankylosing spondylitis; Idiopathic thrombocytopenic purpura; Myasthenia gravis; Sjogren's syndrome; Systemic lupus erythematosus; Systemic sclerosis; Arthritis [psoriasis, rheumatoid arthritis, or osteoarthritis]; Osteoporosis. Comorbidities will be defined as the presence of specific ICD9-CM code OR disease copayment exception code prior the index date OR the presence of certain drug exposure within 6 months before the index date (see Table A3 for details).

- Number of co-medications other than MS therapies (ATC code 5th level six months prior to index date). The number of other individual therapies will be estimated for each patient.
- Number of MS-related hospitalization (three years prior to index date). A hospitalization will be considered as MS-related if a MS diagnosis is included in the discharge referral (first diagnosis, ICD9-CM: 340) (Bezzini 2016).
- Number of hospitalizations (one year prior to index date).
- Number of neurologic visits (one year prior to index date (see table A4 for details)
- Number of brain TAC/RMN dispensing (one year prior to index date; ICD9-CM: 87.03, 87.04, 88,38, 88.91, 92.11)

7.7. Statistical analysis

7.7.1. Drug utilization section

Prevalence and incidence of DMTs use will be calculated using rates by dividing the number of incident/prevalent users with the number of residents living in Tuscany at the 1st January of each corresponding year. Results will be shown as rates per 1,000 inhabitants with 95% confidence intervals (95%CI). Moreover, yearly *DMTs consumption,* will be calculated among prevalent users estimated in an observed years and the total amount of Defined Daily Dose (DDD) dispensed in the corresponding year. The results will be expressed as DDD/1,000 users annually.

7.7.2 Treatment patterns section

7.7.2.1 Patients characteristics & Treatment pattern

Descriptive analyses will be conducted both to assess demographic and clinical characteristics of patients with MS newly treated with DMTs in the different DMTs groups and to estimate the proportion patients falling into the different treatment patterns (see section 7.5), time to events, follow-up time and number of treatment episodes (including type of first - second line treatments) for each DMT drug.

Continuous variables will be described by means and standard deviation or by median and range, while categorical variables will be described by patient counts and percentages.

Finally, the different pattern of use of DMTs at different time point will be plotted by using the Sankey diagram.

7.7.2.2 Determinants of DMTs use and patterns

Demographic and clinical characteristics will be collected at the index date (i.e., the date of the initial treatment episode) as well as at the start date (i.e., date of new treatment episode during the follow-up). The impact of demographic and clinical covariates on the relationship between DMTs specific exposure and treatment patterns will be estimated using recurrent events models and time-varying variables. The results of the analysis will be expressed as Hazard Ratio (HR) with 95% CI (Goel 2010).

7.8. Sensitivity analysis

Analysis of treatment patterns will be conducted by limiting to five years the duration of follow up for all selected patients. Therefore, patients having longer follow up duration will be censored at the end of the fifth year.

7.9. Data management and processing

Data will be extracted from the Oracle database and processed and analyzed using the statistical software R studio version 4.1.0.

7.10. Limitations of the research methods

The main limitation of the study is represented by the absence of clinical evaluation such as the Expanded Disability Status Scale (EDSS). This scale provides useful information about the severity and progression of the disease. In this study, we will use the number of hospitalizations for MS during follow-up as proxy of disease severity. Additionally, in the analysis we will include data on comorbidities and concomitant therapies as a surrogate measure of global health status.

8. ETHICAL CONSIDERATION

The study was approved by the governance board of ARS.

9. DISSEMINATION AND COMMUNICATION STRATEGY

The study findings will be included in a report that will be shared with all the group and experts. The main findings will be included in a manuscript that will be submitted to peer-review international journals. The partial and/or final results of the study will be included in abstracts that will be submitted to the relevant international conferences (e.g., ICPE,

EUPHA, CTRIMS, AAN, EAN). Finally, a report will be included in the annual Tuscany drug report (*Rapporto farmaci della Toscana*).

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11 APPENDIX A

Table A1. MS treatments and dosing schedule

Type of therapy	**Drug name**	**Time of administration**	**Period supply by dispensing claim**	**ATC code/AIC**
Injectable therapy	Interferon beta 1a	Every week	1 month	L03AB07
	Interferon beta 1b	On alternate days	1 month	L03AB08
	Peginterferon beta 1a;	Every 14 days	1 month	L03AB13
	Glatiramer acetate	Daily	1 month	L03AX13
Immunosuppressant	Teriflunomide	Daily	1 month	L04AA31
	Dimethyl fumarate	Daily	1 month	L04AX07
	Fingolimod	Daily	1 month	L04AA27
	Methotrexate	Off-label	Off-label	L01BA01
	Cladribine	First treatment cycle: 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second months; Second treatment cycle: as previously described after 1 year from the first cycle	12 months	L01BB04
Infusive therapy	Natalizumab	Every 4 weeks	1 month	L04AA23
	Alemtuzumab	First treatment cycle: 5 consecutive days of treatment Second treatment cycle: 3 consecutive days of treatment administered 12 months after first cycle	12 months	L04AA34 AIC: 043027
	Ocrelizumab	Every 14 days for first and second dose; following doses every 6 months	6 months	L04AA36

The last column includes the period supplied by a dispensing dose of drug.

Table A2. Cohort Exclusion criteria

Excluded criteria	**Database**	**Type of Code**	**Code**	**Exclusion/censoring criteria**
Malignancy	Pharmacy claim	ATC	L01*	Exclusion criteria: Diagnosis codes 3-years prior the index date and Pharmacy claim 1 prior the index date Censoring during follow-up
	Hospitalization or access to emergency department	ICD-9-CM	140*-239*	
Pregnancy	Hospitalization or access to emergency department	ICD-9-CM	630*-677*	Censoring during follow-up
	Childbirth assistance (CAP),	Case identification in the database		
	Miscarriages databases (IVG)	Case identification in the database		
	Terminations database (ABS)	Case identification in the database		

Table A3. List of comorbidities potentially observed in MS individuals

Comorbidity	**Diseases (ICD-9) ***	**Exemption disease Code**	**Drug claims (ATC code) §**
Hypertension	401–405		C02, C03, C07-C09
Diabetes	250	013	A10
Dyslipidemia	272	025	C10
Mood and anxiety disorders	300.0, 300.2, 296.0, 296.1, 296.04, 296.14, 296.4, 296.44, 296.5, 296.54, 296.6, 296.7, 296.8, 296.2, 296.3, 298.0, 300.4, 311		N06AA01, N06AA02, N06AA04, N06AA11, N06AA12, N06AA17, N06AA21, N06AB03, N06AB04, N06AB05, N06AB06, N06AB08, N06AB10, N06AF03, N06AF04, N06AG02, N06AX06, N06AX11, N06AX16, N06AX21, N06AX23, N05AB12, N05AB06, N05AN01, N03AF01, N03AG01, N03AX09
Chronic lung disease	493, 491, 492, 496	057	R03
Epilepsy	345	017	N03AA02, N03AA03, N03AB02, N03AD01, N03AF01, N03AF02, N03AG01, N03AG04, N03AX09, N03AX12, N03AX15, N03AX14, N05BA09
Migraine	345, 625.4	-	N02CA, N02CC, N02CX
Ischemic heart disease	410-415	-	-
Osteoporosis	733.0		M05BA, M05BB, M05BX04, G03C, G03F, G03XC, H05AA, H05BA, A12A, A11CC
Moderate severe liver disease	456.0 - 456.2, 572.2-572.8	-	
Chronic lymphocytic thyroiditis	240-246		
Inflammatory bowel disease	564.1		
Ankylosing spondylitis	720	054	
Idiopathic thrombocytopenic purpura	287.31		
Myasthenia gravis	358.0		
Sjogren's syndrome	710.2	030	
Systemic lupus erythematosus	710.0	028	
Systemic sclerosis	710.1		
Arthritis	714.0 - 714.3, 714.8, 715	006	
Chronic diseases of liver, pancreas and intestine	555, 556, 571, 572, 577.1-577.9	042	

** Recorded within 3 years prior to the index date; § recorded within 6 months prior to the index date*

Table A4. List of specialist visit observed 1 year prior the index date in MS individuals

Visit name	**Code**	**Tuscany Regional code**
Neurologic visit	89.13	1042
Neurologic visit (follow-up visit)	89.01	1153 2604
Neurologic test	89.15.5	
Computed tomography - head	87.03	3F11, 3F12, 3F13, 3F14, 3F15, 3F16, 3F17
Magnetic resonance	88.91	4E21, 4E22, 4E23, 4E24, 4E25 4E26, 4F113, 4F114, 4F115 4F116, 4F117, 4F118, 4F12
Oligoclonal band test	90.69.2.	6178, 6181
Somatosensory evoked potential test	89.15.4	2425, 1941, 1942, 1943, 1944 1945, 1946, 1947, 1948, 1949 1950

12 APPENDIX B

Figure 1 - Flow chart

Stage 1: DMTs use

1. Patients with MS under treatment with different therapies: drug utilization overview

Output table 1.1 – Prevalent, incident users and DMT consumption (DDD/1000 participants)

Type of therapy	Drug name	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Prevalence													
Injectable therapy	Interferon beta Glatiramer acetate												
Immunosuppressants	Teriflunomide Dimethyl fumarate Methotrexate Fingolimod Cladribine												
Infusive therapy	Natalizumab Alemtuzumab Ocrelizumab												
Incidence													
Injectable therapy	Interferon beta Glatiramer acetate												

Type of therapy	Drug name	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Prevalence													
Immunosuppressants	Teriflunomide Dimethyl fumarate Methotrexate Fingolimod Cladribine												
Infusive therapy	Natalizumab Alemtuzumab Ocrelizumab												
DDD/1000 participants													
Injectable therapy	Interferon beta Glatiramer acetate												
Immunosuppressants	Teriflunomide Dimethyl fumarate Methotrexate Fingolimod Cladribine												
Infusive therapy	Natalizumab Alemtuzumab Ocrelizumab												

Stage 2: *Treatment patterns*

2. Baseline characteristics of new users

Output table 2.1 – Demographic characteristics of new users of DMTs for MS

	Injectable therapy			Immunosuppressants						Infusive therapy			
	Interferon beta	Glatiramer acetate	Total	Teriflunomide	Dimethyl fumarate	Methotrexate	Fingolimod	Cladribine	Total	Natalizumab	Alemtuzumab	Ocrelizumab	Total
Overall, N													
Sex													
Male, N (%)													
Female, N (%)													
Age in years													
mean (± SD)													
median (± IQR)													

Output table 2.2 – Access to healthcare services among new users of DMTs for MS

	Injectable therapy			Immunosuppressants						Infusive therapy			
	Interferon beta	**Glatiramer acetate**	***Total***	**Teriflunomide**	**Dimethyl fumarate**	**Methotrexate**	**Fingolimod**	**Cladribine**	***Total***	**Natalizumab**	**Alemtuzumab**	**Ocrelizumab**	***Total***
Overall, N													
Year of enrollment													
2010													
2011													
2012													
2013													
2014													
2015													
2016													
Hospitalizations													
Patients with at least one event, N (%)													
Number of events per patients, mean (± SD)													
MS-related hospitalizations													
Patients with at least one event, N (%)													
Number of events per patients, mean (± SD)													

Neurologic specialist visit Patients with at least one event, N (%) Number of events per patients, mean (± SD)						

Output table 2.3 – Comorbidities among new users of DMTs for MS

	Injectable therapy			Immunosuppressants						Infusive therapy			
	Interferon beta	Glatiramer acetate	Total	Teriflunomide	Dimethyl fumarate	Methotrexate	Fingolimod	Cladribine	Total	Natalizumab	Alemtuzumab	Ocrelizumab	Total
Overall, N													
Comorbidities, N (%)													
Hypertension													
Diabetes													
Dyslipidemia													
Mood and anxiety disorders													
Chronic lung disease													
Epilepsy													
Migraine													
Ischemic heart disease													
Osteoporosis													
Moderate severe liver disease													
Chronic lymphocytic thyroiditis													
Inflammatory bowel disease													
Ankylosing spondylitis													
Idiopathic thrombocytopenic purpura													
Myasthenia gravis													

	Injectable therapy			Immunosuppressants						Infusive therapy			
	Interferon beta	**Glatiramer acetate**	**Total**	**Teriflunomide**	**Dimethyl fumarate**	**Methotrexate**	**Fingolimod**	**Cladribine**	**Total**	**Natalizumab**	**Alemtuzumab**	**Ocrelizumab**	**Total**
Sjogren's syndrome													
Systemic lupus erythematosus													
Systemic sclerosis													
Arthritis													
Chronic diseases of liver, pancreas, and intestine													

Output table 2.4 – Co-medications other than MS therapies among new users of DMTs for MS

	Injectable therapy			Immunosuppressants						Infusive therapy			
	Interferon beta	**Glatiramer acetate**	**Total**	**Teriflunomide**	**Dimethyl fumarate**	**Methotrexate**	**Fingolimod**	**Cladribine**	**Total**	**Natalizumab**	**Alemtuzumab**	**Ocrelizumab**	**Total**
Overall, N													
Mean (SD), N													
ATC 5 level, N (%)													
0													
1-4													
5+													

3. Treatment patterns

Output table 3.1 – Treatment patterns among new users of DMTs for MS

	Injectable therapy			Immunosuppressants						Infusive therapy			
	Interferon beta	**Glatiramer acetate**	**Total**	**Teriflunomide**	**Dimethyl fumarate**	**Methotrexate**	**Fingolimod**	**Cladribine**	**Total**	**Natalizumab**	**Alemtuzumab**	**Ocrelizumab**	**Total**
Overall, N													
Follow-up time													
mean (± SD)													
median (± IQR)													
Continuers, N (%)													
Discontinuers, N (%)													
Time to discontinuation (days), mean (± SD)													
Time to discontinuation (days), median (± IQR)													
Interrupters, N (%)													
Interruptions per patients, mean (± SD)													
Interruptions per patients, median (± IQR)													
Time to first interruption, mean (± SD)													
Time to first interruption, median (± IQR)													
Mean (± SD)													

	Injectable therapy			Immunosuppressants						Infusive therapy			
	Interferon beta	**Glatiramer acetate**	**Total**	**Teriflunomide**	**Dimethyl fumarate**	**Methotrexate**	**Fingolimod**	**Cladribine**	**Total**	**Natalizumab**	**Alemtuzumab**	**Ocrelizumab**	**Total**
duration (days) of treatment episodes													
Switchers, N (%)													
Switches per patients, mean (± SD)													
Switches per patients, median (± IQR)													
Time to first switch, mean (± SD)													
Time to first switch, median (± IQR)													
Mean (± SD) duration (days) of treatment episodes													
Mixed users (switchers/interrupters), N (%)													
Switches/interruptions per patients, mean (± SD)													
Switches/interruptions per patients, median (± IQR)													
Time to switch/interruptions, mean (± SD)													

	Injectable therapy			Immunosuppressants						Infusive therapy			
	Interferon beta	**Glatiramer acetate**	**Total**	**Teriflunomide**	**Dimethyl fumarate**	**Methotrexate**	**Fingolimod**	**Cladribine**	**Total**	**Natalizumab**	**Alemtuzumab**	**Ocrelizumab**	**Total**
Time to switch/interruptions, median (± IQR) *Mean (± SD) duration (days) of treatment episodes*													

Output table 3.2 – DMT for MS of switched/interrupted (re-started) from all treatment episodes

	Switch/re-start (%)*									
All treatment episodes (N)	**Interferon beta**	**Glatiramer acetate**	**Teriflunomide**	**Dimethyl fumarate**	**Methotrexate**	**Fingolimod**	**Cladribine**	**Natalizumab**	**Alemtuzumab**	**Ocrelizumab**
Interferon B										
Glatiramer acetate										
Teriflunomide										
Dimethyl fumarate										
Methotrexate										
Fingolimod										
Cladribine										
Natalizumab										
Alemtuzumab										
Ocrelizumab										

* on number of all treatment episodes

Output table 3.3 – DMT for MS of switched/interrupted (re-started) from the initial treatment episode

	Switch/re-start (%)*									
Initial treatment episodes (N)	**Interferon beta**	**Glatiramer acetate**	**Teriflunomide**	**Dimethyl fumarate**	**Methotrexate**	**Fingolimod**	**Cladribine**	**Natalizumab**	**Alemtuzumab**	**Ocrelizumab**
Interferon B										
Glatiramer acetate										
Teriflunomide										
Dimethyl fumarate										
Methotrexate										
Fingolimod										
Cladribine										
Natalizumab										
Alemtuzumab										
Ocrelizumab										

* on number of initial treatment episodes

Output table 3.4 – DMT for MS of switched/ interrupted (re-started) from the second treatment episode

	Switch/re-start (%)*									
Initial treatment episodes (N)	**Interferon beta**	**Glatiramer acetate**	**Teriflunomide**	**Dimethyl fumarate**	**Methotrexate**	**Fingolimod**	**Cladribine**	**Natalizumab**	**Alemtuzumab**	**Ocrelizumab**
Interferon B										
Glatiramer acetate										
Teriflunomide										
Dimethyl fumarate										
Methotrexate										
Fingolimod										
Cladribine										
Natalizumab										
Alemtuzumab										
Ocrelizumab										

* on number of initial treatment episodes

Figure 3.1 – Sankey diagram, DMTs treatment patterns during follow-up