2022

Italian Multiple Sclerosis & Related Disorders Register

RISM
The Italian Multiple Sclerosis and Related Disorders Register

Università degli Studi di Bari Aldo Moro

IMN
Istituto di Ricerche Farmacologiche Mario Negri · IRCCS

Sclerosi Multipla onlus
fondazione italiana
un mondo libero dalla SM

Italian Multiple Sclerosis & Related Disorders Register

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Introduction

Italian Multiple Sclerosis & Related Disorders Register

The Italian Multiple Sclerosis & Related Disorders Register (IMS&RD) is one of the main Research Special Projects supported by the Italian MS Society (AISM) and its Foundation (FISM), which was launched with the **aim of creating a multicentric organized infrastructure to collect the data of all patients with MS followed in the various MS centers in Italy (a near population-level).**

THE HISTORY OF THE IMS&RD

Since **2000**, the Italian collection of MS clinical data started at different Italian MS centers in the framework of the Italian Multiple Sclerosis Database Network.
Since **2014**, FISM in collaboration with the University of Bari and the Italian MS clinical centers, promoted and funded the creation of the Italian MS Register **(IMSR)**.
Since **2021**, for greater inclusiveness, the name of the Register has been changed to: Italian Multiple Sclerosis & Related Disorder Register **(IMS&RDR)**. A new module was included for the collection of information on rare forms of demyelinating diseases: demyelinating diseases and Neuromyelitis Optica Spectrum Disorder such as neuromyelitis optica **(NMOSD**) and pathologies associated with the presence of anti-MOG antibodies **(MOGAD).**
Over **168 Italian clinical centers** have joined the project and to date, the IMS&RDR collects the demographic and clinical data of over **77,600 people** in care by Italian clinical centers.
The Register is therefore ready to become a true scientific research tool that can be useful for the development of epidemiological and clinical studies, as well as being a valid tool for health planning by promoting the equity of access to care by comparing the welfare practices of the different centers and to study / evaluate national and local welfare policies.

HIGH-PRIORITY AREAS

The Scientific Committee of the IMS&RDR has identified two high-priority areas:

- **Public Health:** to set up a universal census of patients that is systematically and continuously updated, in order to obtain accurate estimates of prevalence and incidence of the disease at regional and national level in order to improve quality of care, health optimization, social and welfare information, access to healthcare treatments and services.
- **Research**: to gather useful information for the planning of research studies for specific projects. In particular, studies on epidemiology and prognosis, treatment optimization (effectiveness and safety), MS disease course, early and preclinical/subclinical disease stages (CIS and RIS).

INFRASTRUCTURE ORGANIZATION

GOVERNANCE

The governance of the IMS&RDR includes an **Executive Committee** (chaired by FISM and the University of Bari) with the administrative and organizational role and a **Scientific Committee** (which includes clinicians, methodologists, representatives of MS centers, and of the Italian Neurological Society) which oversees the scientific initiatives, promotes specific strategic projects, and approves requests of access to centralized data for further research projects.

The **current Scientific Committee:**

Maria Trojano
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Fondazione Italiana Sclerosi Multipla, Genova

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Francesco Patti
Centro SM, Azienda Ospedaliera-Universitaria, Policlinico Vittorio Emanuela, Università degli Studi di Catania, Catania

OPERATIONAL STRUCTURES

Two operational structures work for the IMS&RDR: the **Technical and Administrative Structure** (TAS) based at FISM in Genoa and the **Technical Methodological Structure** (TMS) based at the Istituto di Ricerche Farmacologiche Mario Negri, IRCCS, Milano.

NETWORKS RELATED TO THE IMS&RDR

MS CLINICAL CENTERS NETWORK

MS centers are recognized as the key component of MS care in Italy. There are approximately 240 MS centers of varying size, and they are often located within public hospital neurology departments. Currently 70% of the Italian MS centers have joined the IMS&RDR.

RESEARCH ASSISTANT NETWORK

With the aim to increase the quality of data collection and data entry, a network of young research assistants (RA) has been trained ad hoc. Currently, 18 Research Assistants are active in 14 Italian Regions (approximately following 100 centers) and are allocated to one or more centers according to their contribution to the project in terms of the number of patients recorded and the geographic distribution. The activities of the RAs include: supporting the start-up phase of the project at the MS centers, supporting the on-time implementation of the project at the MS centers and ensuring a standardized data collection and management.

STAKEHOLDER ADVISORY BOARD(S)

To meet the strategic priorities of the IMS&RDR, relevant stakeholders, including industries, are engaged with an advisory forum. Currently an Industry Advisory Board, including the main pharma companies with interest in MS, is active.

DEDICATED SOFTWARE

During the first years, the IMS&RDR used a client–server solution software (iMed© software), an offline computerized medical folder that needed a periodic upload by clinical centers. At the end of 2016, **a new web-based software** was developed. **From April 2021**, the IMS&RDR is running on **a new modular web-based software** in an exclusive way. Currently the **software release is 3.0**. The software access happens through the reserved area of the website of the project (https://www.registroitalianosm.it/).

SKILLS OF THE NEW PLATFORM

- Patient-centered: the patient is registered only once in the database through a tax code (unique personal identification code). This is a crucial point because the uniqueness of the registered MS subject produces a significant improvement in the pooling of the data in the central database. No double cases are now present in the database.
- Practice: data entry is possible through different devices (PC, mobile, tablet).
- Security: the system respects the standards required by the European Union General Data Protection Regulation (GDPR) 2016/679 and each center enters the data through a personalized password.
- Easy accessibility: an internet access is sufficient.
- Standardized: the database uses standardized codings.
- Printable: it is possible to print a report containing patient information.
- Modular: it is possible to add several modules.

SOFTWARE STRUCTURE OF THE IMS&RDR

The IMS&RDR database collects a minimum data set of variables including crucial information that are useful to characterize the MS patient and other variables included in specific modules such as:

Drugs

This section is dedicated to the patient's treatment history. This module includes the risk-management plan for all the Disease Modifying Treatments (AEs and SAE are codified using MedDRA; Comorbidities are codified using ICD9).

MRI

This section is dedicated to conventional magnetic resonance imaging (MRI) measures (Brain and SC T2 and T1 and Gd+T1 lesion numbers).

Instrumental

This section collects information about: laboratory tests (i.e. virological, immunological, thyroid function and other specific tests), liquor, evoked potentials, EEG, ECG.

COVID-19

This section collects information related to the COVID-19 infection such as: diagnosis, severity, outcome and correlation with DMTs and vaccinations.

NMOSD and MOGAD

This section is dedicated to rare forms of demyelinating diseases: demyelinating diseases and Neuromyelitis Optica Spectrum Disorder such as Neuromyelitis Optica (NMOSD) and pathologies associated with the presence of anti-MOG antibodies (MOGAD).

Pregnancy

This section collects information regarding pregnancy, maternal and foetal outcomes of MS patients and their children.

Pediatric Onset MS

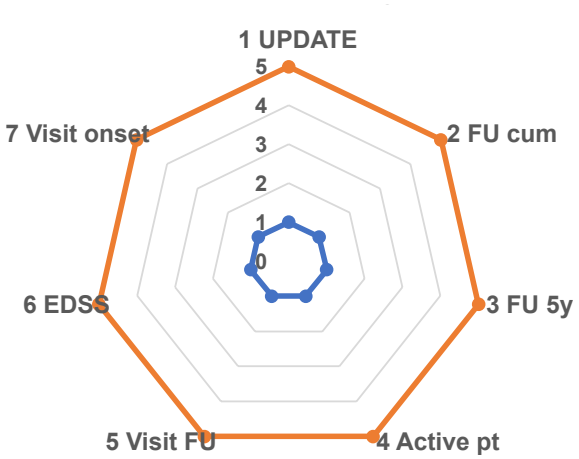
This section collects information on pediatric-onset MS. This module includes information such as: environmental risk factors; vaccinations, cognitive functioning over time and specific MRI features.

DATA MONITORING

Data are **centrally monitored** in order to guarantee a high quality of the information collected. **Centers are periodically contacted** with ad hoc reports with queries on the missing data or inconsistencies among the variables collected. Several tools of quality control have been implemented in order to increase the quality and generalizability of the data collected. Every 2 months per year, all the centers are reached with a report regarding all the data collected and a tailored report regarding each center.
Quality controls regard:

- **dates:** presence/absence, completeness, anomalies and consistency among all the data collected in the dataset
- **completeness:** overall evaluation of the completeness level of the variables included
- **accuracy:** proportion of variables with value corresponding to their range
- **consistency:** congruency with other variables

Moreover, a set of **7 performance indicators** has been identified and adopted with the aim to improve the quality, completeness of the survey, timeliness, generalization, and representativeness of the collected data. For each examined indicator or domain each participating center was awarded with a score of 5 for the highest performance, while lower scores of 4 to 1 were attributed for progressively lower performance. Every 6 months, each participating center receives a report where data and performance indicators of its own center are benchmarked with the whole sample: in this way, each center can assess the most critical performances and the level of improvement with time.
Here the **7 performance indicators** and their graphical representation (radar graph):



1. ***UP DATE:*** *update data*
2. ***FU cum:*** *cumulative follow-up as person/year*
3. ***FU 5y:*** *% of patients with follow-up longer than 5 years*
4. ***Active pz:*** *At least 1 visit in the last 2 years*
5. ***Visit FU:*** *At least 1 visit every 6 months/FU*
6. ***EDSS:*** *At least 1 EDSS evaluation every 6 months/FU*
7. ***Visit onset:*** *At least 1 visit within 1 year from onset*

THE EMA (EUROPEAN MEDICINES AGENCY) INITIATIVE FOR PATIENT REGISTRIES

Real-world data are vital as they offer long-term data collection and allow to evaluate patient's treatment history throughout the disease course. The use of disease registries may provide a better understanding of the effects of comorbidity on effectiveness and safety of disease modifying treatments. EMA is interested in real-world data regarding the post-marketing drug safety assessment (i.e., Post-Authorization Safety Study—PASS). The international data- sharing initiative "Big MS Data Group network" that includes the IMS&RDR, has been recognized as a high quality initiative by EMA, able to provide data for PASS.
Currently, three PASS based on the IMS&RDR are ongoing:

1. An observational study utilizing data from the US Tysabri TOUCH programme and select EU MS Registries to estimate **the risk of progressive multifocal leukoencephalopathy** and other serious opportunistic infections among patients who were exposed to an MS disease modifying treatment prior to treatment with **Tysabri (BIOGEN)**
2. Long-term surveillance of Ocrelizumab (MANUSCRIPT study) treated patients with Multiple Sclerosis **(ROCHE)**
3. Long-term surveillance (CLARION study) of **oral Cladribine** in patients with highly active **RMS (MERCK)**

RESEARCH PROJECTS BASED ON THE IMS&RD DATA

Currently 46 projects approved, 24 completed and 22 ongoing.

The main priority areas of the research projects are:

- **Descriptive Epidemiology** (prevalence, incidence and mortality)
- **Analytical Epidemiology** (risk factors, comorbidity and prognostic factors)
- **MS and RD courses** (benign, RIS, CIS, progressive form, pediatric onset, late onset, aggressive form, NMO-SD and MOGAD)
- **Therapy** (prognostic factors and predictive models of treatment response, treatment adherence, short and long-term treatment effectiveness, safety, comparative effectiveness/safety between treatments, treatment algorithms and switches)

Since 2018 to 2022, over 20 peer-reviewed publications were published on international journals.

Here are reported the title of 22 ongoing projects.

Principal Investigator	TITLE OF THE PROJECT	Priority areas
Mario Alberto Battaglia	**Validate a case definition of multiple sclerosis (MS) using different Electronic (health and social) record: case study on selected provinces of Emilia Romagna Region**	*Descriptive Epidemiology - prevalence*
Giuseppe Fenu	**Changes of clinical and demographic characteristics in patients with MS diagnosis during the various decades between 1983 and 2016**	*Descriptive Epidemiology - prevalence*
Monica Ulivelli	**Immunisation status against major communicable diseases preventable with vaccines, and safety of vaccines, in a cohort of multiple sclerosis patients. An italian multicenter study**	*Descriptive Epidemiology - prevalence*
Roberto Bergamaschi	**Air pollution as a risk factor of multiple sclerosis. An ecological study in the Italian population (The AIRMUS study)**	*Analytical Epidemiology - risk factors*
Marco Capobianco	**Multiple sclerosis disease activity and SARS-COV2 pandemic: a population based study from the Italian MS Registry**	*Analytical Epidemiology - risk factors*
Giovanni Ristori	**Secondary prevention in multiple sclerosis: "Bacille Calmette-Guérin" (BCG) vaccine in people with radiologically isolated syndrome (RIS)**	*Analytical Epidemiology - risk factors*
Jessica Frau	**Evaluation of baseline prognostic factors in a large Italian cohort of patients with multiple sclerosis**	*Analytical Epidemiology, prognostic factors*
Maurizio Leone	**Integrating genetic and phenotypic data from the PROGEMUS data-base and the Italian Multiple Sclerosis registry**	*Analytical Epidemiology - prognostic factors*
Marco Salvetti	**Use of Machine Learning techniques in predicting the course of relapsing-remitting Multiple Sclerosis in individual patients**	*Analytical Epidemiology - prognostic factors*

Francesco Patti	**Clinical and neuroradiological findings in patients with late-onset multiple sclerosis (LOMS)**	*MS and RD courses, late onset*
Emanuele D'Amico	**The influence of pregnancy on neuromyelitis optical spectrum disorder**	*MS and RD courses - NMOSD and MOGAD*
Carla Tortorella	**Clinical and radiological prognostic predictors in Neuromyelitis Optica Spectrum Disorders (NMOSD) and MOG Antibody-mediated Disorders (MOGAD). Evaluation by Italian MS Registry and implementation of a disease-specific dataset**	*MS and RD courses - NMOSD and MOGAD*
Maria Pia Amato	**Evaluating Age-Dependent Efficacy of Multiple Sclerosis Treatments in a Real-Life Cohort**	*Therapy - prognostic factors and predictive models of treatment response*
Damiano Paolicelli	**PROfiling the risk of Severe Adverse Events during sequencing therapiesin patients with multiple sclerosis: an observational cohort analysis based on Italian Multiple Sclerosis Registry**	*Therapy - prognostic factors and predictive models of treatment response*
Matilde Inglese	**The concept of persistence in disability improvement: an application of Markov model to treated patients from the Italian Registry**	*Therapy - prognostic factors and predictive models of treatment response*
Massimo Filippi	**Predictors of response to cladribine in multiple sclerosis patients**	*Therapy - prognostic factors and predictive models of treatment response*
Antonio Gallo	**OCREVID Study:The management of OCRElizumab during the coVID-19 pandemic in Italy**	*Therapy - treatment adherence*
Roberto Bergamaschi	**New generation of sphingosine 1-phosphate (S1P) receptor modulators in clinical practice: a real-world study from the Italian MS Registry**	*Therapy - short and long-term treatment effectiveness*
Giancarlo Comi	**Long-term full responders multiple sclerosis patients treated with first-line disease modifying treatment**	*Therapy - short and long-term treatment effectiveness*
Francesco Patti	**Evaluating the efficacy of Ocrelizumab in Primary PrOgRessive mulTiple sclerosis: a mUlticeNter retrospectIve sTudY (OPPORTUNITY)**	*Therapy - short and long-term treatment effectiveness*
Emanuele D'Amico	**Stop or not the disease-modifying therapies in secondary progressive multiple sclerosis: a comparison study of disability accrual trajectory**	*Therapy - safety*
Tomas Kalincik	**Timing and comparative effectiveness of high-efficacy disease-modifying therapies in childhood-onset multiple sclerosis**	*Therapy - comparative effectiveness / safety between treatments*

Italian Multiple Sclerosis & Related Disorders Register completed project

HETEROGENEITY Study. Are multiple sclerosis (MS) phenotypes influenced by the type of referral MS center?

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INTRODUCTION AND AIMS

Multiple sclerosis (MS) is characterized by phenotypical heterogeneity that may result from the different contributions of demographic and environmental risk factors, and from overall disease severity. However, socio-economic factors and the characteristics of the local MS facilities can also influence the clinical features of patients seen in MS Centers.

This retrospective study included patients with a confirmed diagnosis of MS enrolled in the Italian MS and Related Disorders Register in 2000-2021.

Patients were classified according to the following phenotypes at first visit: clinically isolated syndrome (CIS), relapsing-remitting (RR), primary progressive (PP), progressive-relapsing (PR), and secondary progressive (SP) MS.

Patients' demographic and clinical characteristics were analyzed, along with Centers' structures, capabilities, patient loads, geographic macro-areas, and deprivation index. We computed the odds ratios (OR) for CIS, PP/PR, and SP phenotypes, compared to the RR phenotype, according to selected patients' and Centers' characteristics, using multivariate, multinomial, mixed-effects logistic regression models, adjusted for age, sex, and interval between disease onset and first visit.

RESULTS

The study included 35,243 eligible patients from 106 MS Centers. The OR of presenting more advanced MS phenotypes at first visit, compared to the RR phenotype, significantly diminished in relation to calendar period (OR=0.74 of PP/PR for 2010-2014 period and 2015-2021 vs 2000-2009 periods, and OR=0.50 of SP for 2015-2021 vs 2000-2009 periods). Females had a significantly lower risk than males of PP/PR or SP phenotype. Older age at first visit was associated with CIS (OR=1.37 for ≥ 35 vs <35 years), PP/PR (OR=9.21), and SP (OR=4.53). The risk of longer interval between disease onset and first visit was lower for the CIS phenotype (OR=0.11 for ≥13 vs <13 months), but higher for PP/PR (OR=1.49) and SP phenotypes (OR=10.19). The probability of having SP at first visit was greater in the South (OR=1.86 vs North-West), and the probability of having CIS was higher in the North-East (OR=1.64).

CONCLUSIONS

Differences in the phenotype of MS patients can be only partly explained by differences in the centers' structures, capabilities, and patient loads. The demographic and socio-economic characteristics of MS patients seem to be the main determinants of the phenotypes at first referral.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *Bergamaschi R, Beghi E, Bosetti C, Ponzio M, Santucci C, Lepore V, Mosconi P; Italian Multiple Sclerosis and Related Disorders Register Centers Group and the Scientific Committee of Italian SM and Related Disorders Register. Do patients' and referral centers' characteristics influence multiple sclerosis phenotypes? Results from the Italian multiple sclerosis and related disorders register. Neurol Sci. 2022 Jun 7. doi: 10.1007/s10072-022-06169-7. Online ahead of print*

Demographic, clinical and treatment factors associated with the risk and severity of Covid-19 in people with multiple sclerosis

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INTRODUCTION AND AIMS

The newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV2 or Covid-19) has rapidly spread across the globe becoming a pandemia.
There is a great demand for timely acquired data on the impact of the virus on people with Multiple Sclerosis (PwMS).
Up to 70% of PwMS are treated with disease-modifying therapies (DMTs) which impact the immune response; in turn, these therapeutic agents may expose the patient to increased risk of developing Covid-19 and experiencing worse Covid-19 outcomes than individuals not receiving these agents. Several national and international initiatives have been set up to rapidly collect data about potential risk factors associated with the severity of Covid-19 in PwMS. The majority of these studies have consistently demonstrated male sex, older age, comorbidities, and higher disability as risk factors for a more severe disease course. The role of DMTs in the Covid-19 severity has also been investigated with conflicting results. Different studies showed an increased risk of a severe course for PwMS with a recent use of methylprednisolone and a last therapy with depletive anti-CD20 drugs, while others did not find association between DMT exposure and Covid-19 severity. In addition, some researchers reported a protective role of Interferon beta.
The Italian MS Register offers the possibility to collect data about the complete MS history, in particular data about DMTs exposure and sequences.
In this project, using data collected from the Italian MS Register (IMSR), we conducted for the first time, a case-control study aimed at investigating factors associated with the risk of getting Covid-19. We focused not only on the role of the last administered therapy but also on the potential cumulative effect of previous DMT sequences and on the location where the last treatment was administered (i.e. hospital- or home-based treatment). As a secondary objective, we further assessed the risk factors associated with the severity of Covid-19 outcomes.

RESULTS

We set up a case-control (1-2) study. Cases were PwMS with a confirmed diagnosis of Covid-19, controls were PwMS without a confirmed diagnosis of Covid-19. Both groups were propensity-score matched by the date of Covid-19 diagnosis, the date of last visit and the region of residence. No healthy controls have been included in the present study.
Covid-19 risk was estimated by multivariable logistic regression models including demographic and clinical covariates. The impact of DMTs was assessed in three independent logistic regression models including one of the following covariates: last administered DMT or previous DMT sequences or the place where the last treatment was administered.
A total of 779 confirmed Covid-19 cases were matched to 1558 controls. In all 3 models, comorbidities, female sex and a younger age were significantly associated ($p<0.02$) to a higher risk of contracting Covid-19. Patients receiving natalizumab as last DMT (OR (95% CI): 2.38(1.66-3.42), $p<0.0001$) and those who underwent an escalation treatment strategy (1.57 (1.16-2.13), $p=0.003$) were at significantly higher Covid-19 risk. Moreover, PwMS receiving their last DMT requiring

hospital access (1.65 (1.34-2.04), p<0.0001) showed a significantly higher risk than those taking self-administered DMTs at home.

CONCLUSIONS

Our study provides evidence that among patients with Our study provides evidence that among patients with MS, younger age, being female, having more comorbidities, receiving natalizumab, undergoing an escalating treatment strategy, or receiving treatment at a hospital was associated with being infected with Covid-19. Among patients with MS who were infected with Covid-19, a severe course was associated with increasing age and having a progressive form of MS, while not being on treatment or receiving a beta-interferon agent was protective.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *The risk of Covid-19 in people with Multiple Sclerosis: a case-control study from the Italian MS Register. Oral presentation. ECTRIMS 2021: ONLINE, 13-15 October 2021*
- *Iaffaldano P, Lucisano G, Manni A, Paolicelli D, Patti F, Capobianco M, Brescia Morra V, Sola P, Pesci I, Lus G, De Luca G, Lugaresi A, Cavalla P, Montepietra S, Maniscalco GT, Granella F, Ragonese P, Vianello M, Brambilla L, Totaro R, Toscano S, Malucchi S, Petracca M, Moiola L, Ferraro D, Lepore V, Mosconi P, Ponzio M, Tedeschi G, Comi G, Battaglia MA, Filippi M, Amato MP, Trojano M; Italian MS Register. Risk of Getting COVID-19 in People With Multiple Sclerosis: A Case-Control Study. Neurol Neuroimmunol Neuroinflamm. 2022 Jan 19;9(2):e1141. doi: 10.1212/NXI.0000000000001141*

The use of a roving EDSS reference value to enhance detection of EDSS worsening events: A real world evaluation through the Italian MS Register

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INTRODUCTION AND AIMS

Disease registries are recognized as providing meaningful information on the burden, natural history, and long-term safety and effectiveness of treatments for patients with chronic diseases. Data collected in a register are also useful for observational research on sample populations treated and followed in real-world conditions. The result provided in the study reported below is an indirect validation of the Italian Multiple Sclerosis Register data collection, and support for the usefulness of the standardized collection of data on large groups of subjects, promoting ever greater quality and completeness of data records.

In relapsing-remitting multiple sclerosis patients (RRMS) disability progressively accumulates over time. The aim of this study is to compare, in a real-world setting of the Italian Multiple Sclerosis Register, the cumulative probability of six-month confirmed disability-worsening events using a fixed baseline or a roving EDSS (Expanded Disability Status Scale) according to Kappos's model (Multiple Sclerosis Journal 2018; 24: 963).

RESULTS

Data used for the present analysis derive from the Italian Multiple Sclerosis Register, where, at the time of data analysis, were collected more than 55,000 patients. RRMS patients with at least three EDSS scores at six-month intervals (+/- 90 days) were retrieved together with the following variables: calendar year at inclusion, date of birth, sex, date of disease onset, all reported relapses, EDSS scores, start and end dates for all disease-modifying treatments (DMTs). Patients in the final cohort accumulated person-years of follow-up starting from the date of entering the cohort, i.e. the first EDSS rating, until the earliest date among the events of interest: progression to secondary progressive multiple sclerosis (SPMS), discontinuation of EDSS assessment (defined as a gap of nine or more months between two assessments), death, or end of follow-up. At the end of the selection, the study cohort comprised 7,964 RRMS patients followed for two or more years, with EDSS scores recorded every six months.

Details of the analysis and results obtained are publi-

shed on European Journal of Neurology. Using a fixed baseline EDSS reference, the cumulative probability of six-year overall confirmed disability-worsening events was 33.2%; that of events unrelated to relapse was 10.9% (33% of overall confirmed disability-worsening events). Using a roving EDSS the proportions were respectively 35.2% and 21.3% (61% of overall confirmed disability- worsening events). Results are summarised in the figure below: cumulative probabilities of overall confirmed EDSS-worsening events or confirmed EDSS-worsening events unrelated to relapses using a fixed baseline (first picture) or a roving (second picture) EDSS reference for events occurring six or more months apart. Analyses of the six-year cumulative probability of overall worsening using a roving EDSS reference in strata of patients' baseline characteristics indicated that events were more frequent in older than younger patients, in those with a baseline EDSS score ≥2 than in those with a lower EDSS score, and in those with a longer disease duration than in those with a shorter one.

CONCLUSIONS

This study carried out in a real-world setting such as the Italian Multiple Sclerosis Register, confirms that a roving reference for EDSS evaluation is more accurate than the baseline EDDS score for detecting confirmed disability progression unrelated to relapses in RRMS patients. In a real-world setting, in RRMS patients roving EDSS reference scores appear to be more sensitive for detecting confirmed disability-worsening events unrelated to relapse.

Other tools are needed for assessing disability progression, such as patient-reported and patient-generated outcomes, cognition measures, MRI brain volume changes, optical coherence tomography measures, and new biomarkers, and should be implemented in clinical practice and in experimental settings, to better describe the multifaced impact and evolution of multiple sclerosis.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *Lepore V, Bosetti C, Santucci C, Iaffaldano P, Trojano M, Mosconi P. Detection of disability worsening in relapsing-remitting multiple sclerosis patients. A real-world roving EDSS-Expanded Disability Status Scale reference analysis from the Italian Multiple Sclerosis Register. European Journal of Neurology 2021; 28 (2): 567-578 https://doi.org/10.1111/ene.14589*

Silent progression in an Italian cohort of CIS and relapsing-remitting MS patients

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INTRODUCTION AND AIMS

Disability accrual in multiple sclerosis may occur as relapse-associated worsening (RAW) or progression independent of relapse activity (PIRA). The role of PIRA in early MS is yet to be established. The objective of this multicentre, observational, retrospective cohort study was to investigate the contribution of RAW and PIRA to confirmed disability accumulation in patients with clinically isolated syndrome and early relapsing-remitting multiple sclerosis, assessed within one year from onset and with follow-up >/= 5 years.

RESULTS

Data were extracted from the Italian Multiple Sclerosis Register and related disorders. Confirmed disability accumulation was defined by an increase in Expanded Disability Status Scale score confirmed at 6 months, and classified per temporal association with relapses. Factors associated with progression independent of relapse activity and relapse-associated worsening were assessed using multivariable Cox regression models. A total of 5169 patients were recruited. Over a follow-up period of 11.5 + 5.5 years, PIRA occurred in 1.427 (27.6%) and RAW in 922 (17.8%) patients. PIRA was associated with older age at baseline (HR=1.19; 95CI 1.13-1.25, p<0.001), having a relapsing-remitting course at baseline (HR=1.44; 95CI 1.28-1.61, p<0.001), longer disease duration at baseline (HR=1.56; 95%CI 1.28-1.90, p<0.001), lower Expanded Disability Status Scale at baseline (HR=0.92; 95CI 0.88-0.96, p<0.001), lower number of relapses before the event (HR=0.76; 95CI 0.73-0.80, p<0.001). RAW was associated with younger age at baseline (HR=0.87; 95CI 0.81-0.93, p<0.001), having a relapsing-remitting course at baseline (HR=1.55; 95CI 1.35-1.79, p<0.001), lower Expanded Disability Status Scale at baseline (HR=0.94; 95CI 0.89-0.99, p=0.017), higher number of relapses before the event (HR=1.04; 95CI 1.01-1.07, p<0.001). Longer exposure to disease modifying drugs was associated with a lower risk of both PIRA and RAW (p<0.001). Over the follow-up period, 840 (16.3%) patients fulfilled the algorithmic definition of secondary progressive MS (27.0% of RAW and 41.4% of PIRA subjects). Focusing on patients with one or more confirmed disability accrual, secondary progressive course was associated with older age at baseline (HR=1.28-1.31; 95CI 1.15-1.49, p<0.001), higher expanded disability status scale at baseline (HR=1.38-48; 95CI 1.26-1.55, p<0.001) lower number of relapses before transition (HR=0.91; 95CI 0.85-0.96, p<0.001) and a higher proportion of PIRA events before transition (HR=3.35; 95%CI 2.67-4.22, p<0.001).

CONCLUSIONS

This study provides evidence that in early relapsing-onset multiple sclerosis cohort, PIRA was an important contributor to confirmed disability accumulation. Our findings indicate that insidious progression appears even in the earliest phases of the disease, suggesting that inflammation and neurodegeneration can represent a single disease continuum, in which age is one of the main determinants of disease phenomenology.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *Portaccio E, et al. Progression independent of relapse activity in early multiple sclerosis patients. WCN 2021*
- *Portaccio E, et al. Progression independent of relapse activity in early multiple sclerosis patients and risk of secondary progression: an Italian multicentre study. ECTRIMS 2021*
- *Bellinvia A, et al. Progression independent of relapse activity in paediatric, adult and late-onset multiple sclerosis patients. ECTRIMS 2021*
- *Fonderico M, et al. Relapse-associated worsening and progression independent of relapse activity in an Italian multicentre cohort of early multiple sclerosis patients. ECTRIMS 2021*
- *Portaccio E, Bellinvia A, Fonderico M, Pastò L, Razzolini L, Totaro R, Spitaleri D, Lugaresi A, Cocco E, Onofrj M, Di Palma F, Patti F, Maimone D, Valentino P, Confalonieri P, Protti A, Sola P, Lus G, Maniscalco GT, Brescia Morra V, Salemi G, Granella F, Pesci I, Bergamaschi R, Aguglia U, Vianello M, Simone M, Lepore V, Iaffaldano P, Filippi M, Trojano M, Amato MP; Italian Multiple Sclerosis Register Centers Group. Progression is independent of relapse activity in early multiple sclerosis: a real-life cohort study. Brain. 2022 Mar 24:awac111. doi: 10.1093/brain/awac111. Online ahead of print*

INTEREST: Italian Multiple Sclerosis Registry non interventional retrospective analysis in secondary progressive multiple sclerosis

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INTRODUCTION AND AIMS

The distinction between relapsing-remitting (RR) MS and progressive phenotypes remains a critical challenge for the neurologist in real clinical practice: currently there are not specific parameters or validated biomarkers to address the diagnostic doubt, which remains entrusted to clinical experience. In fact, in clinical practice secondary progressive (SP) MS is typically confirmed retrospectively, following an history of gradual EDSS worsening, after an initial relapsing course, according to the Lublin definition (Lublin F et al. 1996, 2014).

The lack of a single universally accepted definition and the difficulty in distinguishing RRMS and SPMS as a separate entity complicate the management of an already complex pathology. Recently, some studies have proposed an objective definition of SPMS (Lorscheider J et al. Brain 2016). The EXPAND trial, a multicenter study aimed to investigate the efficacy and safety of Siponimod in patient with SPMS, delineated a different definition of SP.

The primary objective of this study is to compare, in terms of diagnostic performances, two data-driven definitions, the one based on a modified version of the Lorscheider algorithm (Iaffaldano P et al. MSJ 2020) (DDA) and the one based on the EXPAND inclusion criteria, with the "neurologist's definition" (ND), currently considered the gold standard in clinical practice. The aim of the study is also to better outline the epidemiological and clinical characteristics of progressive forms: annual incidence and prevalence, treatment strategies, outcome and natural history.

RESULTS

The study has been conducted using longitudinal, retrospectively acquired clinical data extracted from the Italian MS register. Patients with RRMS with a follow-up ≥5 years, with a current age ≥18 years, and with ≥3 EDSS scores recorded were selected from the Italian MS Registry. Annual incidence of SPMS conversion was reported as number of patients converting to SP every 100 patients/year. Three different SPMS definitions have been used. Data-driven definitions based on the Lorscheider's algorithm (DDA) and on the EXPAND trial inclusion criteria were validated, using the ND as gold standard, in terms of calibration, discrimination and goodness of fit by calculating sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), the Akaike information criterion (AIC), the Area Under the Curve (AUC). The overall calibration of th0.05 (DDA=0.55; EXPAND definition=0.57). The AIC (DDA=4301; EXPAND definition=5510) and the R-Square (DDA=0.15 vs EXPAND definition=0.05), were in favour of the DDA, which showed a greater discrimination power (AUC: 0.83 vs 0.65) and was associated with a higher sensibility (77.1% vs 38.0%). Both the definition showed a similar specificity (88.0% vs 91.5%). The PPV and the NPV were both higher using the DDA than those obtained by the EXPAND definition (37.5% vs 29.5%; 97.6% vs 94.0%, respectively). Compared to the gold standard (ND), the data-driven definition based on the EXPAND criteria shows a low sensitivity (38%), because of the exclusion of EDSS worsening events related to relapses. However, these restrictive criteria allow to reach high levels of specificity, with a low risk of identifying as SP patients who are still in the RR phase of the disease. Both criteria are not able to reach levels of sensitivity and specificity that can lead to consider them a valid replacement to the judgment of the neurologist: we have not found a method that can be identified as a possible new gold standard. However, between the two algorithms, the one that is closer to the definition of SP judged by the clinician is that of the DDA, with a sensitivity of 77.1%.

CONCLUSIONS

In conclusion, an accurate definition of SP transition is needed for a timely and efficacious treatment of SPMS patients. Real-world data from the Italian MS Registry suggests that data-driven definitions had a greater ability to capture SPMS transition than neurologist's definition. Moreover, our results indicate that the global accuracy of the DDA seems to be higher than that of a definition based on the EXPAND trial inclusion criteria.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *How to define Secondary Progressive Multiple Sclerosis using different data driven definitions: A validation study from the Italian MS Register. Oral presentation at 51° SIN Congress, Milano 2020*
- *Towards a validated Secondary Progressive Multiple Sclerosis definition: A study from the Italian MS Register. Poster presentation at the 8th JOINT ACTRIMS-ECTRIMS Congress, September 2020*
- *Iaffaldano P, Lucisano G, Guerra T, Patti F, Onofrj M, Brescia Morra V, Zaffaroni M, Pozzilli C, Cocco E, Sola P, Salemi G, Inglese M, Bergamaschi R, Gasperini C, Conte A, Salvetti M, Lus G, Maniscalco GT, Totaro R, Vianello M, Granella F, Ferraro E, Aguglia U, Gatto M, Sangalli F, Chisari CG, De Luca G, Carotenuto A, Baroncini D, Colombo D, Nica M, Paolicelli D, Comi G, Filippi M, Amato MP, Trojano M. Towards a validated definition of the clinical transition to Secondary Progressive Multiple Sclerosis: A study from the Italian MS Register. Mult Scler. 2022 Aug 15:13524585221114007. doi: 10.1177/13524585221114007*

E-MUSIC: Early MUltiple Sclerosis Italian Cohort

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INTRODUCTION AND AIMS

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that is characterized by inflammation, demyelination, and degenerative changes. Most individuals are diagnosed with MS at age 20–40 years. Pediatric-onset MS (POMS), before the age of 18, represents 3-10% of the whole MS population, while late-onset MS (LOMS), after the age of 50, now accounts for 3-5% of all MS diagnosis. Age at onset plays an important prognostic role, not fully understood, and may impact disease course and treatment response. Clinic- and population-based studies suggested that the onset of the progressive phase and time to Expanded Disability Status Scale (EDSS) milestones is an age-dependent phenomenon, independent of the initial course of MS. Nevertheless, predicting disability accumulation just upon chronologic age would be an oversimplification. In both POMS and Adult-Onset MS (AOMS), the strongest predictor for reaching the EDSS milestones is age at clinical onset: the earlier the onset of disease, the younger the age at which the main disability milestones are reached.
Additionally, age at onset influences the response to disease-modifying therapy (DMT). A recent meta-analysis of the main Randomized Clinical Trials (RCTs) demonstrated that the efficacy of DMTs on disability worsening has an inverse correlation with increasing age. As the prevalence of LOMS is increasing, data regarding DMT effectiveness in this group of patients are warranted. This is even more relevant due to comorbidity and possibly higher risks of treatment-related adverse events in this age group. As for the pediatric counterpart, clinical trials in POMS subjects are extremely limited, also due to ethical considerations on the use of placebo owing to highly active disease in this population. Although most of the DMTs are not licensed for POMS, their off-label prescription is increasing in this sub-population. Therefore, benefit to risk balance and treatment decision-making in these extreme age populations present unique age- and disease-related challenges.
Since a sizeable proportion of pediatric and older patients are treated in the real-world setting, registry-based cohort studies represent a major source of data to elucidate the above issues.
The research question, addressed in this multicenter study based on the Italian MS register, was whether and how treatment response differs in three cohorts of RRMS patients defined by age at onset: POMS (≤ 18 years), AOMS (18 - 49 years) and LOMS (≥ 50 years).

RESULTS

We included patients with a relapsing-remitting phenotype, ≥5 years follow-up, ≥3 Expanded Disability Status Scale evaluations and a first neurological eva-

luation within 3 years from the first demyelinating event. Multivariate Cox regression models (adjusted hazard ratio with 95% confidence intervals) were used to assess the risk of reaching a first 12-month confirmed disability worsening and the risk of reaching a sustained Expanded Disability Status Scale of 4.0.
The effect of disease-modifying drugs was assessed as quartiles of time exposure. We found that disease-modifying drugs reduced the risk of 12-month confirmed disability worsening, with a progressive risk reduction in different quartiles of exposure in pediatric-onset and adult-onset patients [adjusted Hazard Ratios in non-exposed versus exposed >62% of the follow-up time: 8.0 (3.5-17.9) for pediatric-onset and 6.3 (4.9-8.0) for adult-onset, p< 0.0001] showing a trend in late-onset patients [adjusted Hazard Ratio = 1.9 (0.9-1.4), p= 0.07]. These results were confirmed for a sustained Expanded Disability Status Scale score of 4.0. We also found that relapses were a risk factor for 12-month confirmed disability worsening in all the three cohorts and female sex exerted a protective role in the late-onset cohort.

CONCLUSIONS

This study provides evidence that sustained exposure to disease-modifying drugs decreases the risk of disability accumulation, seemingly in a dose-dependent manner. It confirms that the effectiveness of disease-modifying drugs is lower in late-onset patients, although still detectable.

PUBLICATIONS AND CONGRESS PRESENTATIONS

Publications

- *Amato MP, Fonderico M, Portaccio E, Pastò L, Razzolini L, Prestipino E, Bellinvia A, Tudisco L, Fratangelo R, Comi G, Patti F, De Luca G, Brescia Morra V, Cocco E, Pozzilli C, Sola P, Bergamaschi R, Salemi G, Inglese M, Millefiorini E, Galgani S, Zaffaroni M, Ghezzi A, Salvetti M, Lus G, Florio C, Totaro R, Granella F, Vianello M, Gatto M, Di Battista G, Aguglia U, Logullo FO, Simone M, Lucisano G, Iaffaldano P, Trojano M. Disease-modifying drugs can reduce disability progression in relapsing multiple sclerosis. Brain.2020 Oct 1;143(10):3013-3024*

Oral presentations

- *Fonderico M. Exposure to disease modifying drugs reduces disability progression in pediatric-, adult- and late-onset relapsing multiple sclerosis: real world data from the early multiple sclerosis italian cohort (E-MUSIC). 50° National Congress of Italian Society of Neurology, Bologna 12-15 October 2019*
- *Fonderico M. Exposure to disease modifying drugs reduces disability progression in pediatric-, adult- and late-onset relapsing multiple sclerosis: real world data from the early multiple sclerosis italian cohort (E-MUSIC). Ectrims 2019, Stockholm, Sweden, 11-13 September 2019*

Assessing the clinical course of pediatric onset multiple sclerosis in different treatment eras: are we really modifying the disease?

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INTRODUCTION AND AIMS

Availability of new disease modifying therapies (DMTs) and changes of therapeutic paradigms have led to a general improvement of multiple sclerosis (MS) prognosis in adults. It is still unclear if this improvement also involves pediatric-onset MS (POMS) patients, whose early management is limited by a low number of approved DMTs and, possibly, other factors, such as cognitive impairment, involvement of the family in therapeutic decisions and risk of low adherence to therapies.

Our aim was to evaluate if prognosis of POMS was getting better over time, in relation to changes in therapeutic and managing standards.

Inclusion criteria were: MS onset before 18 years of age, confirmed MS diagnosis before January 2014 and disease duration ≥3 years at last observation. Exclusion criteria were having primary progressive or undefined MS course, crucial errors in data entry, EDSS score ≥8 one year after the onset of disease, missing diagnosis date and less than two EDSS score evaluations. We compared time to reach persistent disability milestones (EDSS 4.0 and 6.0) by epoch of MS diagnosis (<1993, 1993-1999, 2000-2006 and 2007-2013), adjusting for possible confounders linked to EDSS evaluations (EDSS score evaluations per year, period of

EDSS assessment and disease duration at first EDSS evaluation) and clinical disease activity (age at onset, sex, ARR in the first three years, type of clinical onset, time from onset to diagnosis). We then analysed the difference among the four diagnosis epochs regarding demographic characteristics, clinical disease activity at onset and DMTs management.

RESULTS

At May 2019, the Italian MS Registry included 59,278 patients, of which 4,704 (7.9%) had MS onset before 18 years of age. According to our inclusion and exclusion criteria, we enrolled 3,198 POMS patients, coming from 82 different MS centers in Italy. Distribution of patients among diagnosis epochs was 619 (19%) in <1993, 785 (25%) in 1993-1999, 934 (29%) in 2000-2006 and 860 (27%) in 2007-2013. The mean age of onset was 15.2 years, 69% were female, the median time to diagnosis was 3.2 years, the annualized relapse rate in first one/three years was 1.3/0.6, the mean follow-up was 21.8+11.7 years. The majority of patients were treated with DMTs (88%), of these 40% with high potency drugs (e.g. natalizumab, fingolimod). Considering the whole cohort, only 22% started DMTs in pediatric age, but this percentage increases to 53% in the subgroup with pediatric-diagnosis (1300 patients).
Median survival times to reach EDSS 4.0 and 6.0 were 31.7 and 40.5 years. The cumulative risk of reaching disability milestones gradually decreased over time, both for EDSS 4.0 (HR 0.70 in 1993-1999, 0.48 in 2000-2006 and 0.44 in 2007-2013) and 6.0 (HR 0.72, 0.44 and 0.30). In recent diagnosis epochs, a greater number of POMS patients were treated with DMTs, especially high potency drugs, that were given earlier and for a longer period. Demographic characteristics and clinical disease activity at onset did not change significantly over time. Analyses of the subgroup of patients with pediatric-diagnosis gave similar results.

CONCLUSIONS

In POMS the risk of persistent disability has been reduced by 50-70% in recent diagnosis epochs, probably due to improvement in therapeutic and managing standards. In the coming years, an increase of approved DMTs before 18 years of age and upgrades in drug safety will probably lead to a further improvement of prognosis in this population.

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Clinical characteristics and disease outcomes of late onset multiple sclerosis: a retrospective multicentre study

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INTRODUCTION AND AIMS

Late onset of MS (LOMS), classically defined by the occurrence of the first symptoms after age 50, is relatively infrequent and occurs in less than 10% of patients. Few studies have compared the clinical and demographic characteristics of these patients with young-adult onset MS cases (YOMS), more frequently reporting a progressive course, notoriously associated with more severe disability. However, there is still uncertain information about the clinical outcomes of LOMS, the response to disease modifying treatments (DMTs), and the implication for disease prognosis.

The present project is a multicentre retrospective study that aims to describe the early and late clinical characteristics of LOMS in a large cohort of Italian MS patients, using YOMS as a comparator, in order to evaluate whether the late onset is associated with a more severe disease evolution, also in the relapsing remitting forms.

By using the "Group Based Trajectory Modeling" models, this study describes the disability trajectories of MS patients, also evaluating the characteristics associated to groups with different disability trends over time and the association with LOMS. The data used to define the disability trajectories were obtained from the Italian Multiple Sclerosis Registry. The EDSS scale was used to obtain the disability trajectories in the first 20 visits after diagnosis. The profiles of the patients' groups identified in a specific trajectory were described using a multinomial model by the relative risk ratios (RRRs) and their 95% confidence intervals. The level of statistical significance was set at 5% and the analyses were performed with Stata® 16.

RESULTS

Of the 20,826 patients identified in the registry, 16,159 were eligible for the study. Four groups with different disability trajectories were identified by using the

"Group Based Trajectory Modeling". The group with the most severe EDSS trend (A), was made up of 12.3% of the subjects with mean EDSS > 4 points, which increased over time exceeding EDSS 6; the group with medium severity EDSS trend (B) comprised 21.9% of the sample and showed a change in EDSS score of more than 3 points over time; the larger group (C) with 50.9% of patients reported a constant 2 points in EDSS trend up to 10 visits, with an increase in EDSS in the latest evaluations; finally, the benign group (D) was made up of 14.9% of patients with a low and constant EDSS score over time. The multinomial model shows that the probability of belonging to the groups with the highest severity (A, B, C) is up to 7.0 times higher for the LOMS ($p < 0.001$). In addition, the probability of belonging to groups with greater severity is more associated with male sex and clinical onset with brain stem, spinal cord or multifunctional symptoms.

CONCLUSIONS

Notoriously, MS is a highly heterogeneous disease for clinical, pathogenetic, and neuroradiological features; it is characterized by a high management complexity. From the onset of the disease, it is important to define its clinical characteristics, and in particular to evaluate the predictors of worse long-term clinical outcomes. This project defines how LOMS conditions the disease evolution, by analyzing the disability trajectories. This is also important for the purpose of a tailored choice of DMTs that considers aging, the lower resilience of the nervous system to damage and the frequent concomitance of age-related comorbidities, in addition to the prognostic factors most strictly associated with the disease.

PUBLICATIONS AND CONGRESS PRESENTATIONS

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Assessing early clinical and MRI predictors of treatment response in pediatric multiple sclerosis patients

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INTRODUCTION AND AIMS

Pediatric multiple sclerosis (MS), with disease onset before 18 years of age, represents 3-10% of all MS cases.1 During the last decade, pediatric MS has been increasingly recognized, thus making necessary to identify specific features related to disease onset during childhood and adolescence.

More than 98% of children and adolescents diagnosed with MS follows a relapsing-remitting (RR) course.2 It is characterized by both clinical and MRI evidence of highly active inflammation and remyelination,3 with frequent but highly recoverable relapses early in the disease.4 Among pediatric MS population significant differences in clinical, MRI, and immunological features were observed between early (i.e., by convention, before age 11 years) and late onset pediatric MS patients.

Considering these points, it appeared necessary as first to further characterize this population by analyzing data from a large real-life cohort of pediatric onset MS patients collected in the Italian MS Registry.

In details, we aimed to describe and the natural history of early and late onset pediatric MS and to identify clinical and MRI features at disease onset able to predict a more severe disease course. Then, we aimed to identify early clinical and MRI predictors of three-years treatment response in order to optimize treatment strategies to a better risk-benefit ratio from new highly active drugs. Moreover, we aimed to combine clinical and MRI features recorded over the first year of treatment to identify a score of treatment response specific for pediatric patients.

RESULTS

For the first part of our project, from 3332 pediatric onset MS patients, a cohort of 1993 pediatric onset MS patients was selected from the Italian MS Register.5 Of 1993 pediatric MS cases selected for the final analysis, 172 (9%) were classified as early onset pediatric MS.

A greater proportion of males, isolated brainstem involvement, and longer time interval between first and second clinical episode was observed in early vs late onset pediatric patients. Compared to late onset, early onset pediatric patients took longer time from disease onset to convert to secondary progressive phenotype and to reach three distinct disability milestones (Expanded Disability Status Scale scores of 3, 4, and 6). Recovery from first demyelinating event, time to first relapse, annualized relapse rate during the first 3 years of disease and disease-modifying treatments exposure were independent predictors for long-term disability in early onset pediatric patients. In late onset pediatric patients, isolated optic neuritis, multifocal symptoms or progressive course at disease onset were additional predictors for long-term disability.

To the second aim of our project, we identified the presence of at least three new T2 or Gd+ lesions detected on 1-year MRI scan and the occurrence of at

least 2 relapses during the first year of treatment as independent predictors of treatment failure after 3 years. According to these findings, we grouped risk levels into three classes:
- Group 0: <2 relapses during the first year of treatment and <3 new T2 or Gd+ lesions at 1-year MRI scan;
- Group 1: ≥2 relapses during the first year of treatment or ≥3 new T2 or Gd+ lesions at 1-year MRI scan;
- Group 2: ≥2 relapses during the first year of treatment and ≥3 new T2 or Gd+ lesions at 1-year MRI scan.

According to these features the 79 % of pediatric MS patients resulted in group 0, 19% in group 1 and 2% in group 2. Given the small number of patients in the highest risk category, groups 1 and 2 were also considered together, to define the highest risk group.
High risk vs low risk category had a positive predictive value of 75% and a negative predictive value of 73%, a sensitivity of 44%, a specificity of 91%, and a global accuracy of 68% for identifying patients developing treatment failure over 3 years. Furthermore, pediatric MS patients in low risk category showed a probability of EDSS worsening over 3 years following the first year of therapy of 11% while pediatric MS patients in high risk category of 26%.

CONCLUSIONS

Comparing the natural history of early and late onset pediatric MS in a large, real-life cohort of patients, our study identified several specific features of early onset pediatric MS.
Moreover, this study also points to the critical importance of early treatment in this population, and it adds relevant prognostic information to improve the clinical management of pediatric MS patients.
The combination of clinical relapses with substantial MRI activity appeared as the best predictor of short-term treatment failure and disease progression in pediatric MS patients. The adoption of this simple and pediatric MS-specific score in clinical practice could help clinicians in evaluating treatment failure and in optimizing treatment strategies.

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Early prediction of unfavorable evolution of clinically isolated syndrome (CIS) patients. The RECIS (risk estimate for CIS) study

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INTRODUCTION AND AIMS

The identification of early indicators of multiple sclerosis (MS) prognosis is useful in clinical practice to support early and personalized therapeutic choices.
The aim of the study was to define a prognostic model, which gives in clinically isolated syndrome (CIS) patients an individual risk score (risk estimate for CIS, RECIS), for the early forecast of losing NEDA status (no evidence of disease activity) within 12 months from disease onset, through the analysis of a large set of clinical-demographics (sex, age, type of neurological involvement, EDSS) and instrumental-laboratory (number and site of brain MRI lesions, cerebro-spinal fluid oligoclonal bands - OB, visual and somatosensory evoked potentials – VEPs and SEPs) variables collected at disease onset.

RESULTS

To identify the best prognostic model, we analyzed retrospective data of 221 CIS patients from 4 Italian MS Centres: Gallarate and Pavia (Northern Italy), Florence (Central Italy), Bari (Southern Italy).
After 12 months from CIS onset, 38% of patients displayed EDA.
The variables were included in four different multivariable regression models with 1000 bootstrap replications: 1) a stepwise logistic regression, 2) a Lasso regression with cross-validation approach, 3) a Lasso regression with adaptive approach, and 4) a Lasso regression with plugin approach. According to the best prognostic model, the risk of EDA at 12 months was higher in younger patients and in those patients that at disease onset had MRI infratentorial lesion(s), OBs and abnormal SEPs in lower limbs.
A final score (RECIS score) composed by the variables selected from the best model was reported and the optimal cut-off (0.65) to predict the probability to change the status from NEDA to EDA within one year was estimated. The RECIS score showed good specificity (72%) as a tool for predicting the evolution of CIS: higher RECIS scores were linked to an increased risk of losing NEDA within 12 months. For example, accor-

ding to RECIS score, a 30-year-old patient with oligoclonal bands, abnormal lower limb SEP and infratentorial lesions at MRI at the onset of the CIS will have 85% of probability to reach EDA status within 12 months.

CONCLUSIONS

RECIS score is a simple tool, which can be used at MS onset to predict its evolution within 12 months at a single patient level. This instrument could promote tailored therapeutic decisions in clinical practice setting.

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Predictive factors of disability progression in a large cohort of Italian multiple sclerosis patients

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INTRODUCTION AND AIMS

Multiple sclerosis (MS) is one of the most common causes of neurological disability in young adults globally. It is a chronic degenerative illness and therefore carries a high economic and quality of life burden associated with it. One of the principal objectives in the care of people with MS is, therefore, to reduce the irreversible accumulation of neurological disability.

The diagnosis of progressive MS is clinical and retrospective because based on the patient's history and the neurological exam. In everyday clinical practice, the identification of the change in the disease course is often late and there are no applicable predictors of disability progression.

While group data exist that are prognostic for patients with MS, there are no individually applicable predictors of disease course or severity. This produces considerable anxiety and concern for patients, difficulty for clinicians in providing accurate information to patients and a lack of clear guidance on when and how to treat progressive MS.

Therefore, the objective of the study is to identify the predictive factors of disability progression in RR-MS patients with high disability and patients with a progressive course of MS included in the datasets of the Italian MS registry. The early identification of patients with unfavorable predictive variables will allow treating patients with the new therapies for MS (ocrelizumab and siponimod).

The population of the Italian MS registry is representative of MS population of our Country and includes a large number of patients.

RESULTS

This is a retrospective, longitudinal study that enrolling a large cohort of MS patients of the Italian MS registry with secondary progressive MS (SP-MS), primary progressive MS (PP-MS) and relapsing-remitting MS (RR-MS) with Expanded Disability Disability Status Scale (EDSS) > 4.0 and with an observation period at the centers of at least 6 months. The first visit to the centers is the reference point (baseline) for the beginning of observation. We included patients who performed the first visit in the centers before June 2016. Primary end-point is the disability progression (increase of EDSS score >1.0 point if baseline EDSS < 5.5 and 0.5 if baseline EDSS was > 6.0) sustained and confirmed at the end of follow-up. The 3 groups of patients have been compared during 2-year follow-up to determine predictive factors of disability progression.

We included 5031 patients (3169 female and 1862 male), 1887 with SP-MS, 1096 with PP-MS and 2048 with RR-MS. Of the 5031, 1587 (32 %) had a disability progression after a mean of 15.4 months. The mean of follow-up was 22 months.

At baseline we compared in the three MS groups patients with disability progression vs stable patients. The patients with disability worsening were older at disease onset compared with stable patients in all three groups [SP-MS group: 32 vs 30 years (p:0.001); PP-MS group: 41 vs 39 years (p:0.05); RR-MS group 34 vs 32 years (p:0.005)]. In progressive MS groups patients with disability progression had a shorter disease duration compared with stable patients [SP-MS group: 191 vs 219 months (p<0.0001); PP-MS group: 110 vs 128 months (p:0.004)]. Finally, patients with disability progression had a lower EDSS compared with stable patients in all three groups [SP-MS group: mean EDSS 5.6 vs 5.8 points (p<0.0001); PP-MS group: 5.4 vs 5.7 points (p<0.0001); RR-MS group 4.9 vs 5.0 points (p:0.06)]. In the RR-MS group the patients with disability worsening had also a lower numbers of relapses 1

year before baseline (p:0.018). However, the multivariable analysis not confirmed these data in SP-MS and PP-MS groups. In the RR-MS group the multivariable analysis confirmed the association between disability progression and older age at onset.

CONCLUSIONS

The study did not find strong clinical predictive factors of disability progression. It is necessary to identify fluid biomarkers probably more predictive of disability.

INSPIRA - Italian analysis of the National Multiple Sclerosis Registry Studying the concept of Progression Independent from Relapse Activity

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INTRODUCTION AND AIMS

To date, secondary-progressive multiple sclerosis (SPMS) is diagnosed retrospectively by neurologists, according to Lublin's definition: a history of a gradual disability progression, independent of relapses, after an initial relapsing course. No biological nor clinical markers are available to make more sensitive and reliable the identification of the SP conversion. Thus, it is difficult to establish the exact date of conversion from one course to the other one, mainly because, on a clinical standpoint, the relapsing-remitting (RR) and the SP forms are a continuum of disease with the boundary between them being somewhat indistinct. Recently, objective definitions of SPMS have been proposed. The data driven definitions are based on the application of algorithms to the EDSS score evaluations longitudinally recorded in disease registries or clinical databases.

The majority of the studies so far performed to assess the risk factors for SPMS transition have been conducted on clinical cohorts in which the SPMS definition was based on the subjective judgement of the neurologists. The way the conversion to SPMS is defined might affect the evaluation of risk factors, including the effect of disease modifying therapies (DMTs), potentially associated with the disease course transition.

In this study we compared the risk factors for the transition from RR to SP course in a large cohort of relapsing onset MS prospectively followed-up in the Italian MS Registry, using two different SPMS definitions: the first was based on the subjective decision made by the treating neurologist, and the second was based on a more recently proposed data-driven algorithm. Risk factors for reaching an irreversible EDSS score 6.0 after the SP transition were also evaluated.

RESULTS

On 20th September 2018 the Scientific Committee of the Italian MS Registry granted the approval to this project and the approval of data use. After receiving all the approval needed, we performed the data extraction using the global Italian dataset updated at 31st May 2018. Relapsing onset MS patients (n=19,318) were extracted from the Italian MS Registry. Risk factors for SPMS and for reaching irreversible EDSS 6.0, after SP transition, were estimated by using multivariable Cox regression models.

Two SPMS definitions were used:

1. Neurologist Definition (ND). A definition based on the subjective decision made by the neurologists according to the Lublin criteria for SP. For this definition the date of SP conversion, entered by the neurologists in the (iMed®) software, was used.
2. Data-Driven Algorithm (DDA). An algorithm based on a previous published definition with some modifications: a 3-strata progression magnitude (1.5-point increase if the baseline EDSS was 0, 1.0-point increase if the baseline EDSS was 1.0-5.5, 0.5-point increase if the baseline EDSS was > 5.5) with a minimum EDSS score of 4.0 and a minimal pyramidal FS score of 2.0 at the time of conversion to SPMS confirmed at 3 months and at the end of follow-up (last EDSS score ≥ 4.0; last pyramidal FS score ≥ 2.0). In order to reduce the impact of transient EDSS modifications due to relapses, all the EDSS scores collected during a relapse (± 30 days) were excluded.

SPMS identified by the DDA (n=2,343, 12.1%) were older, more disabled and with a faster progression to severe disability ($p<0.0001$), than those identified by the ND (n=3,868, 20.0%). In both groups, the most consistent risk factors ($p<0.05$) for SPMS were a multifocal onset, an age at onset >40 years, higher baseline EDSS score and a higher number of relapses; the most consistent protective factor was the DMT exposure. DMT exposure during SP, did not impact the risk of reaching irreversible EDSS 6.0.

CONCLUSIONS

Our study suggests that a more objective definition of SPMS based on a DDA is more reliable to identify patients with a more aggressive SP course in comparison to a retrospective subjective judgment of the treating neurologist. These findings can help to select more homogeneous population of SPMS patients to be included in future clinical trials or observational studies to evaluate the effect of DMTs during the SP phase of the disease. Moreover, our results provide further insights on the most robust prognostic factors associated to the SPMS transition confirmed by using different criteria of SPMS. It is noteworthy that the results also confirm the role of DMT exposure in reducing this risk, but not in preventing the disability accumulation after the transition to SPMS.

National MS registries, such as the Italian MS Registry, represent formidable tools to provide important information on the disease course and the effect of DMTs in the different phases of the disease.

PUBLICATIONS AND CONGRESS PRESENTATIONS

Publications

- *The full paper which present the complete results of this study has published by Multiple Sclerosis Journal and an Editorial has been dedicated to our work*
- *Iaffaldano P, Lucisano G, Patti F, Brescia Morra V, De Luca G, Lugaresi A, Zaffaroni M, Inglese M, Salemi G, Cocco E, Conte A, Ferraro D, Galgani S, Bergamaschi R, Pozzilli C, Salvetti M, Lus G, Rovaris M, Maniscalco GT, Logullo FO, Paolicelli D, Achille M, Marrazzo G, Lovato V, Comi G, Filippi M, Amato MP, Trojano M; Italian MS Register. Transition to secondary progression in relapsing-onset multiple sclerosis: Definitions and risk factors. Mult Scler. 2021 Mar;27(3):430-438. doi: 10.1177/1352458520974366*
- *Lorscheider J. When does a heap become a heap? Mult Scler. 2021 Mar;27(3):329-330. doi: 10.1177/1352458520988459*

Congress

- *Defining the risk factors for the conversion to secondary progressive multiple sclerosis: a retrospective cohort study of the Italian MS Register. 35th ECTRIMS Congress, Stockholm, Sweden 11-13 September 2019. This presentaion has been selected for the congress highlights*
- *Evaluating the risk factors for the conversion to secondary progressive multiple sclerosis: a retrospective cohort study of the Italian MS Register. 50°congresso SIN Bologna 2019*

Assessing efficacy and safety of treatments in progressive multiple sclerosis

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INTRODUCTION AND AIMS

Except for Ocrelizumab, previous phase-III randomized controlled trials largely failed in finding benefit of disease modifying drugs (DMDs) among patients affected by primary progressive multiple sclerosis (PPMS). Consistently with these findings, most of the Real word studies drove to the same conclusion, finding no substantial differences between treated and untreated patients in the real clinical setting. However, some recent results highlighted that a sustained exposure to DMDs, especially when the drug is administered at a young age and in patients with inflammatory activities, may exert a protective role, reducing the risk of hard disability milestones.

RCTs suffer from low generalizability and explore the effect of therapy for a time-window that rarely covers more than two years. Moreover, variables like the duration of DMT exposure or the delay in treatment initiation are not evaluated in the setting of clinical trials, but they may be crucial in the real-world setting.

In the absence of previous licensed therapeutic options, DMTs have been used off-label in PPMS patients, and registry-based cohort study represents a major source of real-world data to elucidate the above issues.

We hypothesized that, among PPMS patients, those who had active disease at baseline or experienced superimposed relapses during follow-up might benefit from DMT. Moreover, to better understand the effects of DMTs, we evaluated the type of DMT, the delay in treatment initiation and the duration of DMT exposure.

RESULTS

Using the Italian MS Registry, we selected PPMS patients with at least three EDSS evaluations and three years of follow-up. Study baseline was defined as the first EDSS evaluation for untreated patients and the date of the first DMT initiation for treated patients.

Of the 1,139 patients we included (629 females, mean ± Standard Deviation [SD] baseline age 48.3 ± 11.1 years, mean EDSS score 4.1 ± 1.8), 746 (65%) received a DMT during the follow-up. In the whole sample, after a mean (SD) follow-up of 11.8 (± 6.3) years, 438 (38%) reached the EDSS 7.0. In the multivariable Cox regression models, the use of DMT, analysed as dichotomous variable, did not influence the risk of reaching EDSS 7 (aHR = 1.09, 95% CI 0.88-1.36, p = 0.417). However, in patients with superimposed relapses, DMT exposure significantly reduced the risk of reaching EDSS 7 (aHR = 0.61, 95% CI 0.42-0.87, p =0.007). Moreover, we found that, among good responders to DMT, those who persisted on treatment had the most beneficial effect (aHR = 0.45, 95% CI 0.29-0.71, p = 0.001).

These results have been confirmed after propensity-score matching.

CONCLUSIONS

This study suggests that inflammatory activity may be a modifiable component of long-term disability outcomes in PPMS patients. Moreover, in PPMS patients who have inflammatory activity during follow-up, longer exposure to DMT may increase the beneficial effect of treatment.

To optimize treatment decision-making in PPMS further profiling of the best candidates to treatment is needed.

PUBLICATIONS AND CONGRESS PRESENTATIONS

Oral presentations

- *Fonderico M. "Disease modifying treatment may delay time to wheelchair in primary progressive multiple sclerosis: a real-life cohort". 8th Joint ACTRIMS-ECTRIMS MEETING, 11th September 2020*
- *Fonderico M. "Disease modifying treatment may delay time to wheelchair in primary progressive multiple sclerosis: a real-life cohort". 51° National Congress of Italian Society of Neurology, Milan, 28-30th November 2020*

Exploring phenotype and recovery from relapses in relapsing-remitting multiple sclerosis patients: old versus new disease-modifying therapies

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INTRODUCTION AND AIMS

The clinical course of relapsing remitting multiple sclerosis (RRMS) is largely determined by the frequency, severity, and recovery of relapses, which show extreme variability during the disease course.

A high frequency and severity of relapses, particularly in the first 2 years, have been described as strong predictors of greater disease burden in terms of disability accumulation and treatment failure(s).

The relapse phenotype has not been fully investigated and it has not been included as parameter in clinical trials to verify a disease modifying therapy (DMT) and scarce data with controversial results are available from small studies

The incomplete recovery, defined by the persistence of neurologic deficits after a relapse, has been observed in 34–59% of relapses.

The disease characteristics that could be associated to the degree of recovery have only been found in few real-world studies and cannot be generalized.

Notably, the degree of recovery from the first relapse in a patient's course was shown to predict the time to disability progression and the time to transition into secondary progressive MS, although the association of each relapse phenotype to the degree of recovery has not been characterized unequivocally.

The primary study outcome was the evaluation of first relapse phenotype in RRMS patients generally and based on the first-line DMT prescribed during the first 5 years of treatment. Next, incomplete recovery (sequelae) based on relapse phenotype and the type of first-line DMT was determined.

Ancillary, the role of each relapse phenotype on the probability to obtain an EDSS score ≥ 4.0 during the

entire follow-up period (the first 5 years of therapy unless the DMT was discontinued earlier) was investigated.

RESULTS

All the 2,676 patients fulfilled the required criteria. The first-relapse phenotype of 712 relapses was determined. Being female and higher number of relapses before diagnosis were associated with higher risk of relapse in the 5-year period (HR = 1.3, 95%CI 1.07–1.46; p = 0.005 and HR = 1.1, 95%CI 1.06–1.15; p < 0.001, respectively) whilst older age at the time of first DMT prescribed (HR = 0.98, 95% CI 0.98–0.99; p < 0.001) to a lower risk. The pyramidal phenotype was associated with higher age and baseline EDSS score. Older age correlated also with worse sequelae (proportional OR = 1.02, 95%CI 1.01–1.04; p = 0.004), as the occurrence of a second relapse before the DMT starting (proportional OR = 1.72, 95%CI 1.01–2.92; p = 0.044). The pyramidal phenotype, adjusted for age and other phenotypes was associated to a 1.95-fold higher risk of severe or moderate sequelae (proportional OR = 1.95 95%CI 1.35–2.80; p < 0.001).

CONCLUSIONS

The characterization of different relapse phenotypes from early phases of RRMS and the first DMT prescribed should be considered a determinant of therapeutic choice.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *First relapse phenotype and recovery in naïve relapsing remitting multiple sclerosis patients undergoing first-line therapies: an Italian Registry study. Submitted to European Journal of Neurology as original paper*
- *First relapse phenotype and recovery in naïve relapsing remitting multiple sclerosis patients undergoing first-line therapies: an Italian Registry study. Submitted to EAN 2022 as poster*
- *First relapse phenotype and recovery in naïve relapsing remitting multiple sclerosis patients undergoing first-line therapies: an Italian Registry study. Presented as poster to ECTRIMS 2021 and accepted as a poster for the next AAN congress 2022*
- *Zanghì A, Avolio C, Amato MP, Filippi M, Trojano M, Patti F, D'Amico E; Italian MS register. Real world comparison of teriflunomide and dimethyl fumarate in naïve relapsing multiple sclerosis patients: Evidence from the Italian MS register. Mult Scler Relat Disord. 2022 Jan 2;58: 103489. doi: 10.1016/j.msard.2022.103489. Online ahead of print*

Retrospective pilot study on long-term Cladribine effects in patients with relapsing remitting multiple sclerosis or clinically isolated syndrome

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INTRODUCTION AND AIMS

The aim of this Italian pilot study call CLARINET-MS study is to explore the feasibility of the retrospective approach for evaluating effectiveness in subjects previously treated with Cladribine and then followed as per clinical practice.

The CLARINET-MS study assessed the long-term effectiveness of cladribine tablets by following patients with multiple sclerosis (MS) in Italy, using data from the Italian MS Registry. Real-world data (RWD) from Italian MS patients who participated in cladribine tablets randomised clinical trials (RCTs; CLARITY, CLARITY Extension, ONWARD or ORACLEMS) across 17 MS centres were obtained from the Italian MS Registry. RWD were collected during a set observation period, spanning from the last dose of cladribine tablets during the RCT (defined as baseline) to the last visit date in the registry, treatment switch to other disease-modifying drugs, date of last Expanded Disability Status Scale recording or date of the last relapse (whichever occurred last). Time-to-event analysis was completed using the Kaplan–Meier (KM) method. Median duration and associated 95% confidence intervals (CI) were estimated from the model.

RESULTS

Time span under observation in the Italian MS Registry was 1–137 (median 80.3) months. In the total Italian patient population (n = 80), the KM estimates for the probability of being relapse-free at 12, 36 and 60 months after the last dose of cladribine tablets were 84.8%, 66.2% and 57.2%, respectively. The corresponding probability of being progression-free at 60 months after the last dose was 63.7%. The KM estimate for the probability of not initiating another disease-modifying treatment at 60 months after the last dose of cladribine tablets was 28.1%, and the median time-to-treatment change was 32.1 (95% CI 15.5–39.5) months.

CONCLUSIONS

CLARINET-MS provides an indirect measure of the long-term effectiveness of cladribine tablets. Over half of MS patients analysed did not relapse or experience disability progression during 60 months of follow-up from the last dose, suggesting that cladribine tablets remain effective in years 3 and 4 after short courses at the beginning of years 1 and 2, and in some patients with RRMS and relapsing SPMS up to 60 months after the last dose.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *Patti F, Visconti A, Capacchione A, Roy S, Trojano M; CLARINET-MS Study Group. Long-term effectiveness in patients previously treated with cladribine tablets: a real-world analysis of the Italian multiple sclerosis registry (CLARINET-MS). Ther Adv Neurol Disord. 2020 Jun 10;13:1756286420922685. doi: 10.1177/1756286420922685. eCollection 2020*

Big Multiple Sclerosis Data (BMSD) network

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INTRODUCTION AND AIMS

In 2013, five MS registries (Italian MS registry - formerly known as iMEDweb network, SMSReg of Sweden, MSBase based in Australia, OFSEP of France and the Danish MS registry) started to evaluate the potential, usefulness and potential paths of collaboration and/or pooling of data for research on the diagnosis, epidemiology and treatment of MS – the Big MS Data Network (BMSD).

RESULTS

A feasibility phase was carried out between 2014 and 2015. This feasibility evaluation comprised the following steps: registries descriptions; registries comparison in terms of governance structure, data collection tools and data storage systems, availability of key variables for MS research.
The governance of the BMSD network has been established as follows: a steering committee composed by the principal investigator of each involved registry; a data management subcommittee composed by data analysts involved in the data management of each dataset; a statistical analysis committee composed by statisticians and project leaders of the research projects.
At the end of the feasibility phase was decided to launch three demonstrator projects in order to test the capability to pool data which come from different sources, working also on the harmonization of the data structure, outcomes definitions and data analysis.
The following were the title of the projects along with the leading registry: Very long term effectiveness of DMTs in multiple sclerosis - Italian MS Registry; Discontinuation frequencies of DMTs - Swedish MS Registry; Efficacy of DMTs in progressive MS – MSBase.
Here are reported the objectives and the main results obtained from these projects.
1. Very long term effectiveness of DMTs in multiple sclerosis - Italian MS Registry: The aim was to evaluate the impact of the time interval from disease onset to the first DMT on the treatment effect on long-term disability accumulation.
Four study outcomes were evaluated: 3- and 12-month Confirmed Disability Worsening (CDW) and assignment of either irreversible EDSS 4.0 or EDSS 6.0.
In the first step of our analysis, four Cox regression models were used to estimate the risk of reaching each of the 4 outcomes. The time from disease onset

to the first DMT start was included as quintiles and the first quintile was included as reference class.
In the second step of this analysis, propensity score (PS) matching was used to enable pairwise comparisons among patients grouped by the time from disease onset to the first DMT start.
The final cohort obtained by applying the inclusion criteria was composed by 11,871 RRMS patients.
A 3- and 12-month confirmed disability worsening event and irreversible EDSS 4.0 and 6.0 scores were reached by 7,062 (59.5%), 4,138 (34.9%), 3,209 (31.1%) and 1,909 (16.5%) patients, respectively.
The risk of reaching all the disability outcomes was significantly lower ($p<0.0004$) for the 1st quintile patients' group. These data represent the largest RRMS cohort with the longest follow-up ever analysed to determine the long-term effectiveness of the early initiation of DMTs. Our results indicate that the optimal time to start DMTs in MS to prevent long-term disability accumulation is within 12 months of disease onset.
2. Discontinuation frequencies of DMTs - Swedish MS Registry: The objective of this study was to describe treatment interruption and discontinuation in the BMSD network. Information on 269,822 treatment episodes in 110,326 patients from 1997 to 2016 were retrieved. Treatment stop was defined as a clinician recorded DMT end for any reason and included treatment interruptions, switching to alternate DMTs and long-term or permanent discontinuations. The incidence of DMT stopping across the full observation period was lowest in fingolimod (19.7 per 100 person-years (PY) of treatment; 95% CI 19.2–20.1), followed by natalizumab (22.6/100 PY; 95% CI 22.2–23.0), IFNb (23.3/100 PY; 95% CI 23.2–23.5). Of the 184,013 observed DMT stops, 159,309 (86.6%) switched to an alternate DMT within 6 months. DMT stopping reasons and rates were mostly stable over time with a slight increase in recent years, with the availability of more DMTs. The results suggest that discontinuation of MS DMTs is mostly due to DMT properties and to a lesser extent to risk management and a competitive market.
3. Efficacy of DMTs in progressive MS – MSBase: The objective was to identify subgroups of SPMS patients with similar longitudinal trajectories of EDSS over time. Longitudinal EDSS scores were modelled by a latent class mixed model (LCMM), using a nonlinear function of time from the first EDSS visit with an EDSS value of 3 to 4.
A total of 3613 SPMS (66.2% females; 39.1% from France, 24.4% from Italy, 19.6% MSBase, 16.9% Sweden). LCMM detected 3 different subgroups of patients with a mild, a moderate and a severe disability trajectory. Median time to EDSS 6 was 12.2, 5 and 1.7 years, for the 3 groups respectively. Patients with the "severe" disability time course were younger ($p<0.001$) and with a shorter disease duration at baseline ($p<0.001$). Heterogeneity among the four Registries was also observed ($p<0.001$) with a higher frequency of patients with milder MS in the French (39.2%) and Swedish (43.9%) registries. We observed a higher frequency of moderate MS in the Italian (59.6%) and MSBase (55.6%) registries. These results indicate that for the treatment of SPMS and in the design of
future clinical trials, with time to confirmed EDSS progression as the primary endpoint, the existence of heterogeneous classes of patients could have important implications.

CONCLUSIONS

In conclusion, the results obtained by the BMSD network provide evidence that data sharing among MS registries and databases is feasible and can provide enough statistical power to detect the impact of treatment on disability outcomes over the long term and to select specific sub-population that may need a more tailored treatment approach.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *Iaffaldano P, Lucisano G, Butzkueven H, Hillert J, Hyde R, Koch-Henriksen N, Magyari M, Pellegrini F, Spelman T, Sørensen PS, Vukusic S, Trojano M. Early treatment delays long-term disability accrual in RRMS: Results from the BMSD network. Mult Scler. 2021 Sep;27(10):1543-1555. doi: 10.1177/13524585211010128*
- *Hillert J, Magyari M, Soelberg Sørensen P, Butzkueven H, Van Der Welt A, Vukusic S, Trojano M, Iaffaldano P, Pellegrini F, Hyde R, Stawiarz L, Manouchehrinia A, Spelman T. Treatment Switching and Discontinuation Over 20 Years in the Big Multiple Sclerosis Data Network. Front Neurol. 2021 Mar 17;12:647811. doi: 10.3389/fneur.2021.647811*
- *Signori A, Lorscheider J, Vukusic S, Trojano M, Iaffaldano P, Hillert J, Hyde R, Pellegrini F, Magyari M, Sorensen PS, Spelman T. Heterogeneity on long-term disability trajectories in secondary progressive MS patients-a latent class analysis from big MS data network. Presented to ECTRIMS congress 2021. Multiple Sclerosis Journal 2021 Oct 1, Vol. 27, No. 2_ Suppl, pp. 213-214*
- *Website: https://bigmsdata.org*

Comparative effectiveness of initial treatment choices for multiple sclerosis: a multicentre study

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INTRODUCTION AND AIMS

Multiple sclerosis (MS) therapies have changed considerably over the last several decades, with the approval of oral disease modifying therapies (DMTs) following the demonstration of efficacy and safety for the treatment of the relapsing forms of MS (RRMS).
This multicenter, observational, retrospectively acquired, and propensity adjusted cohort study utilized RRMS-naïve patients from the Italian MS Register who started either injectable or oral first-line DMTs between January 1, 2010, and December 31, 2017, to evaluate the impact on disability outcomes in patients.

RESULTS

Enrolled patients were divided into two groups, namely the injectable group (IG) and the oral group (OG). Of a cohort of 11,416 patients, 4,602 were enrolled (3919 in the IG and 683 in the OG). The IG had a higher rate of women (67.3% vs 63.4%, $p < 0.05$) and a lower mean age (36.1 ± 10.9 vs 38.9 ± 11.8, $p < 0.001$). The event time to first relapse demonstrated a lower risk in the OG (HR = 0.58; CI 95% 0.48–0.72, $p < 0.001$). However, no differences were found between the two groups with respect to the risk of CDP (HR = 0.94; CI 95% 0.76–1.29, $p = 0.941$), while a lower risk of DMT was found in the OG (HR = 0.72; CI 95% 0.58–0.88, $p = 0.002$) for the event time to discontinuation.

CONCLUSIONS

Real-world data from the Italian MS Register suggests that first-line oral DMTs are associated with a lower risk of experiencing a new relapse and of therapy discontinuation compared to injectable DMTs. From this project derived three scientific publications, focusing on first line DMT's comparison.

PUBLICATIONS AND CONGRESS PRESENTATIONS

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Autologous Hematopoietic Stem Cell Transplantation for Secondary Progressive Multiple Sclerosis: a comparative study with matched control patients from the Italian Multiple Sclerosis Register

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INTRODUCTION AND AIMS

Treatment of secondary progressive multiple sclerosis (SPMS) remains unsatisfactory. Uncontrolled evidence suggests that autologous hematopoietic stem cell transplantation (AHSCT) can be effective in people with active SPMS, as a result of the profound immune ablative effect of CNS-penetrant chemotherapy. In this study, we compared the effect of AHSCT with that of other anti-inflammatory disease modifying therapies (DMT) on long-term disability worsening in active SPMS.

Methods: We collected data from the Italian-Bone-Marrow-Transplantation-Study-Group and the Italian-Multiple-Sclerosis-Register. Patients were considered eligible if treatment had been started after the diagnosis of SPMS. Disability worsening was assessed by the cumulative proportion of patients with a 6-months confirmed-disability-progression (CDP) according to the Expanded-Disability-Status-Scale (EDSS) score. Key secondary endpoints were the EDSS time-trend after treatment start and the prevalence of disability improvement over time. A linear mixed model with a time*treatment group interaction was used to assess the longitudinal EDSS time-trends. Time to CDP was assessed by means of proportional hazard Cox regression models. Prevalence of improvement was estimated according to a modified Kaplan-Meier estimator and compared between groups by bootstrapping the area under the curve.

RESULTS

79 AHSCT-treated patients and 1975 patients treated with other DMT were matched to reduce treatment selection bias using propensity-score and overlap weighting approaches. Time to first CDP was significantly longer in transplanted patients (HR= 0.50; 95% CI: 0.31, 0.81; p=0.005), with 61.7% of transplanted patients free from CDP at 5 years. Accordingly, EDSS time-trend over 10 years was higher in patients treated with other DMT than in AHSCT- treated patients (+0.157 EDSS points per year compared to -0.013 EDSS points per year; interaction p<0.001). Patients who underwent AHSCT were more likely to experience a sustained disability improvement: 34.7% of patients maintained an improvement (a lower EDSS than baseline) 3 years after transplant versus 4.6% of patients treated by other DMT (p<0.001).

CONCLUSIONS

The use of AHSCT in people with active SPMS is associated with a slowing of disability progression and a higher likelihood of disability improvement compared to standard immunotherapy.

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Clinical effectiveness of different natalizumab interval dosing schedules in a large Italian population of patients with multiple sclerosis

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INTRODUCTION AND AIMS

Natalizumab (NTZ; Tysabri) is a humanized anti-α4 integrin monoclonal antibody that blocks lymphocyte adhesion to endothelial cells, thereby preventing their migration to the central nervous system (CNS) and reducing inflammation. The NTZ safety and efficacy in relapsing-remitting multiple sclerosis study (Safety and Efficacy of Natalizumab in the Treatment of Multiple Sclerosis- AFFIRM study) showed that NTZ, compared with placebo, was able to reduce the annualized relapse rate (ARR) by 68% relative to placebo, the accumulation of new or enlarging hyperintense lesions by 83%, 12-week sustained disability progression by 42% and 24-week sustained disability progression by 54% over 2 years. Since its approval in 2006/2007, NTZ has demonstrated higher efficacy in reducing the progression of MS compared with second-line drugs, although safety issues have imposed a strict clinical surveillance. The potential occurrence of progressive multifocal leukoencephalopathy (PML) in NTZ-treated patients has prompted an intense search for the best strategy to reduce such a serious complication and to prevent the clinical and radiological relapses associated to NTZ discontinuation, in particular the risk of a clinical rebound. In this regard, an early study has proved that a progressive return of subclinical MRI activity may occur after approximately 7 weeks from the last NTZ infusion in patients with MS, suggesting

that the therapeutic window of NTZ could be larger than that approved based on clinical trials. Thus, a reasonable delay of time between infusions could provide advantages in terms of safety (i.e., reduced risk of PML), likely without exposing patients to a risk of MS relapse. Therefore, in real-world clinical practice, the neurologists of Italian MS centers across the country have begun to treat patients with MS using various extended interval dosing schedules.

This multicenter retrospective observational study aims to provide additional information on NTZ effectiveness in the real-world clinical practice and to evaluate the therapeutic durability of different extended dosing strategies (standard interval dosing [SID] versus extended interval dosing [EID]) in a large Italian population of patients with MS.

RESULTS

At the extraction date, 5,231 patients with relapsing-remitting MS (RR-MS) who had received NTZ from 1 June 2012 to 15 May 2018 in 30 Italian MS centers were recruited. A total of 2,092 patients (mean age of 43.2±12.0 years, 60.6% were women) met the inclusion criteria and were finally enrolled. The remaining 3139 patients were excluded because of missing data. We found that 1,254 (59.9%) patients received NTZ according to SID and 838 (40.1%) according to EID. EID patients had longer disease duration and higher EDSS before starting NTZ compared with SID. Moreover, the percentages of patients drug-naïve and of patients treated with immunosuppressant drugs before starting NTZ treatment were higher in the EID compared with the SID group.

At 12 and 24 months after start of NTZ, no differences in terms of annualized relapse rate (ARR) and of expanded disability status scale (EDSS) were found between the two groups. No statistically significant differences in terms of percentage of patients reaching NEDA-2, progression index (PI) and confirmed disability improvement (CDI) were found between the two groups.

Overall, at 24 months, the percentage of patients positive to the John Cunningham virus (JCV) slightly increased from 26.9% to 29.5% (p=0.14), with a significantly higher JCV index compared with baseline (p<0.001). Stratifying according to the two different administrations schedules, after 24 months, both SID and EID groups showed a significant increase of JCV index values compared with baseline (1.1±1.4 vs 1.4±1.1, p<0.001 and 2.0±0.9 vs 2.2±1.5, p<0.001, respectively). At 24 months, in the patients with baseline EDSS scores available (n=1,651, 78.9% of 2,092), the cumulative probabilities of 12-month and 24-month confirmed EDSS worsening (CEW) were 14.3% and 11.6%, respectively, with worsening defined as an increase in EDSS score of ≥1.0 point. When worsening was defined as an increase of ≥2.0 points, the cumulative probabilities were 8.1% and 6.1%, respectively. No differences in terms of CEW were found between SID and EID. In the overall population, 689 (41.7% of 1,651) patients had a baseline EDSS score 0.0–2.0, 432 (41.5% of 1040) in SID and 257 (41.6% of 611) in EID. Among these patients, the cumulative risk of confirmed transition to an EDSS score ≥3.0 was 7.3% at 12 months and 8.1% at 24 months. Among the 643 (38.9% of 1651) patients with a baseline EDSS score of 2.5–3.0, 402 (38.7% of 1,040) in SID and 241 in EID (39.4% of 611), the cumulative risk of confirmed transition to an EDSS score of ≥4.0 was 12.4% at 12 months and 13.2% at 24 months with a trend towards a higher probability to proceed from 2.0 to 3.0 to >4.0 EDSS score in the EID (16.9% at 12 months and 16.9% at 24 months) versus the SID (12.4% at 12 months and 13.6% at 24 months) group. For the 319 (19.3% of 1,651) patients with a baseline EDSS score of ≥4.0, 206 (19.8% of 1040) in SID and 113 (18.5% of 611) patients in EID, the cumulative risk of confirmed transition to an EDSS score of ≥6.0 was 18.4% at 12 months and 23.6% at 24 months with no differences between SID and EID patients. Moreover, Kaplan-Meier estimates for the first relapse occurrence, CEW of 1 point and CEW of 2 points showed no statistically significant differences between the two groups.

CONCLUSIONS

The use of NTZ with an extended interval schedule showed similar effectiveness compared with SID. Unchanged clinical efficacy of EID schedule may raise the question of a possible advantage in terms of tolerability and safety.

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Risks associated with wash-out duration when switching from fingolimod to cell-depleting agents

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INTRODUCTION AND AIMS

Decisions regarding the duration of washout periods between disease-modifying therapies (DMTs) in multiple sclerosis (MS) patients need to take both the risk of disease reactivation and safety issues regarding overlapping immunological mechanisms of action into account.

Fingolimod is an oral DMT, approved for the treatment of highly active relapsing-remitting (RR) MS. It induces sequestration of B and T lymphocytes in secondary lymphoid organs, with decrease of absolute lymphocyte counts (ALC) to 20%– 30% of baseline values between days 3 and 7 of treatment initiation. After FTY discontinuation ALC progressively increase and return within the normal range for approximately half the patients by six weeks and to approximately 80% of pre-treatment values by 12 weeks.

Following the publication of case-series and case-reports on the lack of response to alemtuzumab, rituximab and ocrelizumab following FTY withdrawal, it has been hypothesized that their efficacy may be incomplete if commenced before ALC has recovered, possibly because sequestered lymphocytes are protected from cell-depleting agents. Studies on larger cohorts, however, have found both alemtuzumab and rituximab to be an effective option after FTY withdrawal,

and that disease activity during alemtuzumab did not correlate with the baseline ALC or with the washout interval.
Seeing the kinetics of lymphocyte reconstitution, it is plausible to think that the risk of incomplete lymphocyte recovery is greater in the first 6-8 weeks following FTY discontinuation. This potential risk, however, has to be balanced with the risk of return of disease activity/persisting disease activity or even of a rebound syndrome, starting from 4 weeks after ceasing FTY.
Given the growing complexity of treatment choices it is important to gather information on drug- sequencing and on the most appropriate washout duration between drugs.
Aim of this study was, therefore, to assess the risk of relapses following FTY discontinuation and the initiation of a B/T cell-depleting agent (aletumzumab, cladribine or anti-CD20 agents – ocrelizumab and rituximab) in relation to the duration of washout, using data from the Italian MS Register.

RESULTS

Out of 61,625 patient records available at the time of data extraction (on November 14th 2019), a total of 329 patients were included in the analysis (226F, 103M; mean age 41±10 years).

Ninety patients relapsed during the washout period and 72 during the subsequent cell-depleting therapy. During the cell-depleting treatment, the incidence rate ratio (IRR) for a relapse was significantly greater in patients with a washout-period of 12-17 (IRR (95%CI): 2.4 (1,1-5,5); p=0.037) and >/=18 weeks (6.0 (2.8-12.7); p<0.001) compared to the reference period (<6 weeks).
The multivariable Cox analysis showed that the time to a relapse (hazard ratio – HR) was significantly influenced by the occurrence of relapses during FTY treatment [HR (95%CI): 1.4 (1.2-1.7); p<0.001]. Moreover, washout durations of 6-11, 12-17 and >/=18 weeks were associated with a higher risk of a relapse in comparison to washout durations shorter than 6 weeks [HR: 3.7 (1.1-12.7), p=0.041; 5.7 (1.6-20.6), p=0.008; 15.9 (4.6-54.6), p<0.001, respectively].

CONCLUSIONS

Results of the present study underline the risk of disease reactivation, which increases with the duration of washout when switching from FTY to lymphocyte-depleting agents.
Real-life studies on large populations and on MS registries such as this one can provide useful data to guide clinicians on strategies for treatment switches.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *Risks associated with wash-out duration when switching from fingolimod to cell-depleting agents. Poster (P0913), MSVirtual2020 ECTRIMS, Multiple Sclerosis Journal 2020; 26: (S3) 552–659*
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Retrospective study to evaluate the long-term impact of different treatment strategies on disability sclerosis. Italian IMedWeb MS Registry. RE.LO.DI.MS Study

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INTRODUCTION AND AIMS

The increase in disease-modifying drugs (DMDs) allows individualization of treatment in relapsing multiple sclerosis (RMS); however, the long-term impact of different treatment sequences is not well established. This is particularly relevant for MS patients who may need to postpone more aggressive DMD strategies.
To evaluate different therapeutic strategies and their long-term outcomes, measured as relapses and confirmed disability progression (CDP), in MS 'real-world' settings.
The multicentre, observational, retrospectively acquired cohort study evaluates the long-term impact of different treatment strategies on disability outcomes in patients with RMS in the Italian MS Register.

RESULTS

We evaluated 1152 RMS-naïve patients after propensity-score adjustment. Patients included were receiving: interferon beta-1a (IFN-β1a) 44 µg switching to fingolimod (FTY; IFN-switchers; n = 97); FTY only (FTY-stayers; n = 157); IFN-β1a only (IFN-stayers; n = 849). CDP and relapses did not differ between FTY-stayers and IFN-switchers [HR (95% CI) 0.99 (0.48–2.04), p = 0.98 and 0.81 (0.42–1.58), p = 0.55, respectively]. However, IFN-stayers showed increased risk of relapses compared with FTY-stayers [HR (95% CI) 1.46 (1.00–2.12), p = 0.05].

CONCLUSIONS

The ideal treatment option for MS is becoming increasingly complex, with the need to balance benefit and risks. Our results suggest that starting with FTY affects the long-term disease outcome similarly to escalating from IFN-β1a to FTY.

PUBLICATIONS AND CONGRESS PRESENTATIONS

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Early-aggressive treatment algorithm versus classical escalation therapy in relapsing multiple sclerosis

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INTRODUCTION AND AIMS

The most important goal of multiple sclerosis (MS) therapy is the prevention of long-term disability accumulation. The therapeutic scenario for relapsing–remitting MS (RRMS) has widely expanded during the past 20 years. Choosing the MS therapy has become increasingly complex, due to the difficulties in weighing the risk/benefit ratio of several different available disease modifying therapies (DMTs). To date, except for individuals expressing poor clinical and radiological features at baseline, the most applied treatment algorithm for early naïve MS is based on an escalation strategy. According to this approach, patients start with safe moderate-efficacy DMTs and switch to high-efficacy immunotherapies with a more complex safety profiles in case of first treatment failure. The superiority of high-efficacy DMTs, such as natalizumab, alemtuzumab, ocrelizumab, cladribrine, mitoxantrone or fingolimod, in reducing measures of clinical and MRI disease activity in comparison to the traditional first-line MS therapies, such as interferon (IFN) ß, glatiramer acetate (GA), teriflunomide or dimethylfumarate have been consistently proven by different randomized clinical trials (RCTs) and/or observational studies. Moreover, indirect comparisons from extension arms and subgroup analyses of randomized trials suggest that high-efficacy therapies are associated with improved control of relapse activity when initiated earlier after MS onset. Whether patients initiating therapy with high-efficacy DMTs derive a greater long-term benefit on disability accumulation than those who start with moderate-efficacy agents, remains a matter of debate. Recent observational studies showed evidence that early initiation of highly effective therapy in RRMS may provide more benefit that an escalation approach in decreasing the risk of developing secondary progression and disability accrual, at least in a medium-term of 5-6 years of follow-up.

In this study, we compared the long-term effect of an early versus a late start (escalation approach) of high-efficacy DMTs on disability trajectories in a large population of naïve RRMS who started the first treatment within the first year from the disease onset and longitudinally followed up to 10 years.

RESULTS

According to the Registry rules, on February 5th 2018, the Scientific Committee of the Italian MS Registry granted the approval to conduct this project and extract and use the registry data. Patients with relapsing onset MS, with a follow-up duration of at least 5 years, a first visit within 3 years from disease onset and at least 3 Expanded Disability Status Scale (EDSS) score evaluations after the first DMT start were extracted from the Italian MS Registry database. Patients meeting the eligibility criteria were divided in two groups: the early intensive treatment

(EIT) group if their first treatment was one of the six high-efficacy DMTs (natalizumab, alemtuzumab, mitoxantrone, fingolimod, cladribine or ocrelizumab) and the escalation treatment (ESC) group if their first therapy was a moderate-efficacy DMT (IFN ß, GA, teriflunomide, dimethylfumarate or azathioprine) followed by escalation to a high-efficacy DMT, due to a lack of efficacy, after at least one year of treatment.

Patients were 1:1 propensity score (PS)-matched for characteristics at the first DMT. The disability trajectories were evaluated by applying a longitudinal model for repeated measures. The effect of early versus late start of high-efficacy DMT was assessed by the mean annual EDSS changes compared to baseline values (delta-EDSS) in EIT and ESC groups.

Longitudinal clinical data of 53,010 patients from 89 MS centers were available in the Italian MS Registry at the time of data extraction (November 2019). After applying the inclusion and the exclusion criteria we retrieved 2,702 RRMS patients from 62 Italian MS centers. In this cohort, 365 patients received a treatment classifiable as EIT approach, while a larger sample of 2,337 patients was treated according to the ESC strategy. The PS matching procedure produced 363 pairs of patients. Mean annual delta-EDSS were all significantly ($p<0.02$) higher in the ESC group compared to the EIT group. In particular, the mean estimated delta-EDSS differences between the two groups tend to increase from 0.1 (0.01-0.19, $p=0.03$) at 1 year, to 0.30 (0.07-0.53, $p=0.009$) and to 0.64 (0.35-0.93, $p<0.001$) at 5 and 8 years respectively, while at 10 years (the last year of study observation) it was 0.67 (0.31-1.03, $p=0.0003$). The maximum mean delta-EDSS difference was 0.72 (0.40-1.04, $p<0.001$) measured at 9 years.

CONCLUSIONS

The results of our real-world study indicate that the long-term disability trajectories are more favorable with an EIT strategy than with moderate-efficacy DMTs followed by escalation to high-efficacy DMTs. Although further studies are necessary, especially to establish the long-term safety risks of the EIT approach, these findings may drive the treatment decisions of physicians, in particular in the cases of naïve patients with poor prognosis factors at the onset of disease.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *Comparison of disability trajectories in relapsing Multiple Sclerosis patients treated with early intensive or escalation treatment strategies. MSVIRTUAL2020: 8th joint ACTRIMS-ECTRIMS Meeting. Virtual Meeting 11-13 September 2020*
- *Comparing disability trajectories in relapsing Multiple Sclerosis patients treated with early intensive or escalation treatment strategies. 51° Congresso della Società Italiana di Neurologia. Congresso virtuale.28-30 novembre 2020*

Profiling treatment choices in MS during two different eras: a real world assessment in the Italian MS Registry

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INTRODUCTION AND AIMS

The treatment options for people with multiple sclerosis (MS) have expanded dramatically during the past 20 years. The objective of these disease-modifying treatments (DMTs) is the prevention of further relapses and accumulation of disability. In the European Union neurologists and patients can currently choose from different licensed DMTs, making it increasingly diffi-

cult for patients and their physicians to choose between treatments at disease onset and in case of non-response to treatment.
The main objectives of this study were: to evaluate the changes in therapeutic approach in 2 different treatment epochs and to compare the clinical efficacy of the different first line choices in treatment-naïve relapsing-remitting (RR)MS patients.

RESULTS

On 14th December 2016 our research group, on behalf of 18 Italian MS centers, notified to the Italian MS Register the study protocol. Subsequently, on 23rd March 2017 the Scientific Committee of the Italian MS Register granted the approval to this project and the approval of data use.
By using data obtained from the Italian MS Register we extracted two cohorts of naïve RRMS patients receiving the 1st DMT:
- 1st cohort: first DMT prescription during the 2 years prior to the marketing of Teriflunomide in Italy (Old Era);
- 2nd cohort: first DMT prescription during the 12 months after the marketing of Dimethylfumarate in Italy (New Era).
Predictors of treatment choice have been evaluated by regression models with an unstructured correlation-type matrix to account for the hierarchical nature of the data (patients clustered within geographic area (north, center and south)). The intra-class correlation coefficient (ICC) was calculated to assess the variation in the use of treatment choice among geographic area; a greater impact of the geographic area is shown by higher ICC values. The relapse risk during the course of the first DMT prescribed in the New Era cohort, stratified by the baseline EDSS score (≤3, >3), has been evaluated using a Poisson regression model.
The first cohort (Old Era) was composed by 1,795 RRMS patients, 422 of whom received Glatiramer Acetate (GA) as first DMT. The presence or lack of comorbidities, the age and the disease duration at the time of the 1st DMT prescription were all factors associated with the first treatment choice when only injectables DMT were available as first line drug. Furthermore, the variation in the use of treatment choice among geographic area as impact of ICC was comprised between 2 and 20%. Interferon Beta was more frequently prescribed as first-line DMT in the south of Italy.
The second cohort was composed by 1,097 MS patients, 338 of whom with first line Oral DMTs. No significant predictors were associated to the dimethylfumarate choice. Teriflunomide was more significantly prescribed in patients with low rates of comorbidities, who were older and with a longer disease duration than patients who received the injectables or the dymethylfumarate treatment. Variation in the use of oral treatment choice among geographic areas as impact of ICC was 7%.
The relapse risk during the course of the first DMT prescribed in the New Era cohort was evaluated in two separated models based on the baseline EDSS score. In patients with a baseline EDSS > 3 a higher relapse risk was found in younger patients. In patients with a baseline EDSS ≤ 3 increasing age and disease duration at the treatment start, and choice of dimethylfumarate were associated with a lower risk of relapse. A higher number of relapses before the first DMT prescription and the choice of teriflunomide as first DMT were associated with an increased risk of relapse.

CONCLUSIONS

Our results indicate that in Italy GA was used more frequently in patients older and with more comorbidities than patients treated with IFNB before the introduction of oral first-line DMTs.
The new first line oral DMTs have been more frequently used in patients without comorbidities in comparison to injectable DMTs. This latter finding was more pronounced in patients treated with teriflunomide. In less-disabled patients (EDSS ≤3) the use of dimethylfumarate was associated with a reduced risk of relapse in comparison to teriflunomide.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *The present work has been presented as Poster at at XLVIII Congresso Nazionale SIN, Napoli 14-17 ottobre 2017*

EPID-MS Evaluation of the drivers of the therapy switch in active RRMS and active SPMS patients

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INTRODUCTION AND AIMS

The clinical course of MS is increasingly considered as a continuum but the classification in classic clinical phenotypes remains fundamental in clinal practice and academic world. Approximately 85% of people with MS are initially diagnosed with the relapsing-remitting form of MS (RRMS), typically between the ages of 20 and 40 years. Primary progressive MS (PPMS) is not considered as a separate entity but part of the spectrum of progressive disease, including the challenging definition of secondary progressive MS (SPMS). (Lublin F et al. 1996, 2014).

Moreover, different recently published therapeutic studies have included patients with relapsing MS (RMS), a term that comprises active RRMS and SPMS patients, and consequently health authorities have granted the authorization of DMTs to patients with RMS. (Lublin et al. 2020, Comi et al. 2021, Filippi M et al. 2022).

The therapeutic scenario for MS patients has widely expanded during the past 20 years but a large proportion of patients continue to experience clinical and subclinical disease activity. (Gross RH and Corboy JR, 2019)

Reasons for suboptimal response to DMTs may vary considering the highly heterogeneous nature of the disease, but switching patients who experience a suboptimal treatment response on one DMT to a more effective option is crucial to minimize the accumulation of disability and delay disease progression (Weinstock-Guttman B et al. 2022) In patients who experience first-line treatment failure (Kalincit T et al. 2015) or who have a high risk of reactivation of the disease after discontinuation of treatment, it is reasonable to consider highly effective therapies (Iaffaldano P et al. 2015).

The primary objective of this study is to assess clinical and therapeutic characteristics of the RMS patients in the Italian Multiple Sclerosis Registry (IMSR), in order to evaluate the percentage of patients switching DMT due to disease activity, defined as occurrence of relapses, and to describe the different drivers of treatment patterns during the disease course.

RESULTS

The study has been conducted using longitudinal, retrospectively acquired clinical data extracted from the Italian MS register.

Patients with RRMS and SPMS disease course, with ≥ 5 year follow-up, with a first medical visit within 3 years from the disease onset and at least 3 Expanded Disability Status Scale (EDSS) score evaluations were extracted from the IMSR database.

In order to define the MS phenotypes, we used the following definitions:

- RRMS definition according to McDonald 2010 criteria;
- SPMS definition: data-driven SPMS definitions based on a modified version of the Lorscheider's algorithm (DDA) (Iaffaldano P et al. 2020);
- Active RRMS and SPMS: RRMS and SPMS with at least one relapse in the last 2 years of follow up available;
- All RMS: Population of all patients with active RRMS and active SPMS (as above).

To evaluate the impact of disease activity in the choice of the next therapeutic strategy, we have first determined the proportion of patients with relapses occurred during treatment, then we evaluated how these disease activity measures can influence the treatment switch.

The effect of demographic, clinical and DMT exposure on the risk of treatment switch was assessed using multivariable logistic regression models.

The role of DMTs exposure was assessed in 2 different models including: last recorded DMT or last DMTs grouped according to their efficacy and mechanism of action (MoA) (moderate efficacy (ME), high efficacy (HE) DMTs, anti-CD20 drugs).

The final cohort was composed of 21,174 RRMS and 1153 SPMS patients. Using a clinical definition, we identified 4161 RR (19.7%) and 578 SP (50.1%) active patients, of whom 2694 (56.8 %) switched DMT. RMS patients were significantly younger (median (IQR) years: 36.50 (29.10-44.80) years vs 39.60 (32.80-48.00), $p<0.0001$), less disabled (median (IQR) EDSS score: 2.00 (1.00-3.50) vs 2.50 (1.50-4.00), $p<0.0001$), more frequently affected by a RR disease course (89.8% vs 85.2%, $p<0.0001$) in comparison with not active patients. The multivariable logistic regression model performed revealed that Alemtuzumab (OR 0.08 95% CI 0.02-0.37), Natalizumab (OR 0.48 95% CI 0.30-0.76), Ocrelizumab (OR 0.1 95% CI 0.02-0.45) and Rituximab (OR 0.23 95% CI 0.06-0.82) were protective factors against treatment switch due to relapses in comparison with patients exposed to Interferon beta products. Our model also revealed that the use of HE DMTs was a protective factor against the treatment switch due to a relapse (OR 0.43 95% CI 0.31-0.59), especially considering anti-CD20 drugs (OR 0.14 95% CI 0.05-0.37) in comparison with the use of ME DMTs.

CONCLUSIONS

In conclusion, our results showed that clinical disease activity is an important trigger of treatment switch in RMS patients. HE DMTs, especially those with anti-CD20 MoA, significantly reduce the risk of disease activity in RMS.

PUBLICATIONS AND CONGRESS PRESENTATIONS

- *38th Congress of ECTRIMS - OCTOBER 2022: "Drivers of therapy switch in relapsing multiple sclerosis: Poster Session 1; Session Date: 26.10.2022; Presenting Time: 16:30 h; Poster Number: P371*
- *52° SIN Congress - Milano 2022: "Evaluation of determinants of therapy switch in Relapsing Multiple Sclerosis: a study from the Italian MS Register" - Session Title: Poster Session Multiple Sclerosis 1*

Notes

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