2024

RISM
The Italian Multiple Sclerosis and Related Disorders Register

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

IMN
ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

NETWORK OF THE ITALIAN MS CLINICAL CENTERS

Italian Multiple Sclerosis and Related Disorders Register

Promoted and Funded by the
Italian Multiple Sclerosis Foundation
in collaboration with the
University of Bari and the Italian MS clinical centers

SCLEROSI MULTIPLA ETS
fondazione italiana

un mondo **libero** dalla SM

Italian Multiple Sclerosis and Related Disorders Register

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Published by:
Italian Multiple Sclerosis Foundation - ETS
Via Operai, 40 - 16149 Genoa, Italy

Design and layout:
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Printed by **Ditta Lang Srl** - Genoa, September 2024

ISBN 978-88-7148-181-4

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ITALIAN MULTIPLE SCLEROSIS AND RELATED DISORDERS REGISTER

The Italian Multiple Sclerosis and Related Disorders Register is supported by the contribution of FISM, the Italian "5x1000" Income tax, donations, and the following companies:

ALEXION AstraZeneca Rare Disease

Bristol Myers Squibb

MERCK

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Roche

SANDOZ

VIATRIS

Mario Alberto Battaglia
FISM Congress 2024

Maria Trojano
FISM Congress 2024

Paola Mosconi
FISM Congress 2024

Designation of Prof. Trojano as honorary member of ECTRIMS, London 2016

Research Assistant online meeting, July 2024

Annual Big MS Data Meeting, Belfast 2024

2nd BigMS Workshop "Statistical methods to address specific RWE questions" - Bari, June 2023

Introduction

Introduction

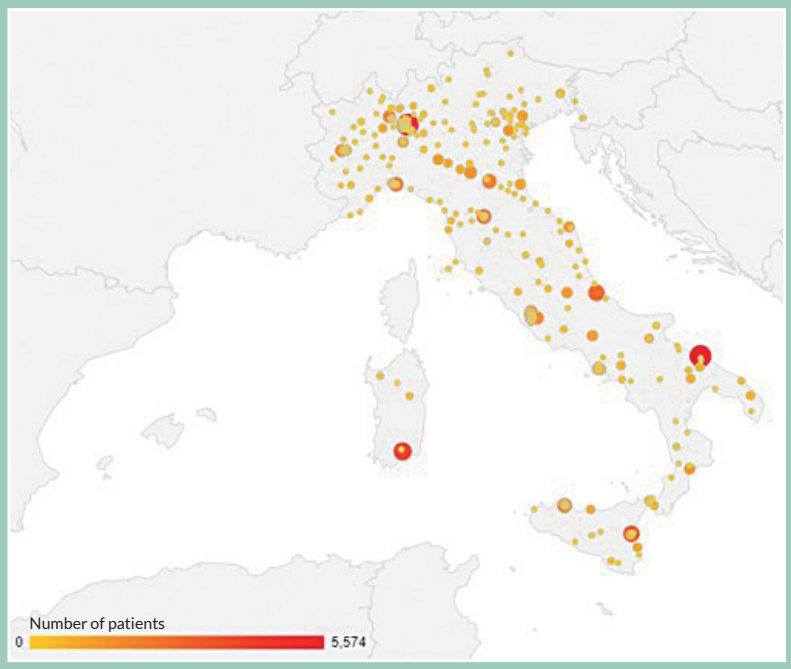
Italian Multiple Sclerosis and Related Disorders Register Project

The Italian Multiple Sclerosis and Related Disorders Register (RISM) 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) (1).**

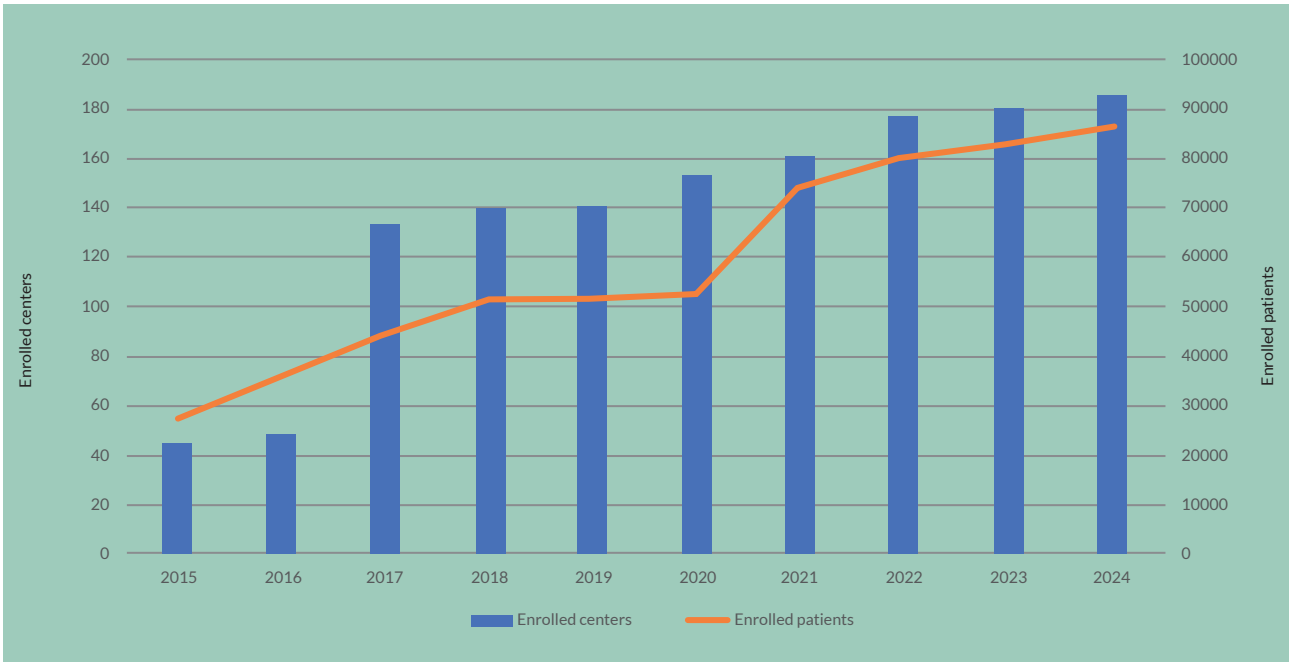
THE HISTORY OF RISM

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 (RISM).
Since 2021, for a greater inclusiveness, the name of the Register has been changed to: Italian Multiple Sclerosis and Related Disorders Register (RISM). A new module has been included for the collection of information on rare forms of demyelinating diseases: Neuromyelitis Optica Spectrum Disorder (NMOSD) such as neuromyelitis optica and pathologies associated with the presence of anti-MOG antibodies (MOGAD). Approximately 190 Italian clinical centers have joined the project (see appendix 1 for the full list of participating centers) and to date, RISM collects the demographic and clinical data of over 89,500 people in care by Italian clinical centers (data updated at July 2024).
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 a public health valid tool for 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.

Distribution of patients and clinical multiple sclerosis centers in Italy. The proportional area chart (circles) represents the number of patients for each MS clinical center



1. Trojano M, Bergamaschi R, Amato MP, et al. The Italian multiple sclerosis register. Neurol Sci. 2019 Apr; doi: 10.1007/ s10072-018-3610-0



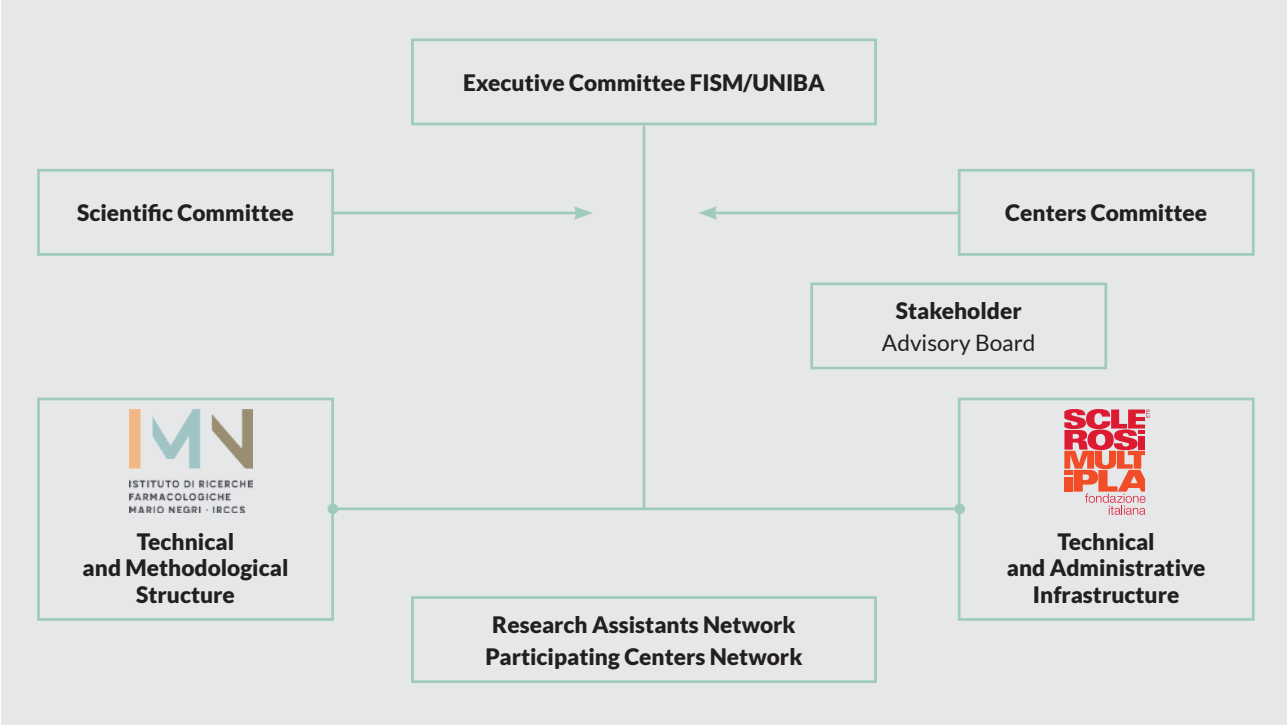
Enrolled centers and patients in the RISM Project from 2015 to 2024

HIGH-PRIORITY AREAS

The Scientific Committee of RISM 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 pre-clinical/subclinical disease stages (CIS and RIS).

INFRASTRUCTURE ORGANIZATION



GOVERNANCE

The governance of RISM 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.

OPERATIONAL STRUCTURES

Two operational structures work for RISM: the **Technical and Administrative Infrastructure** (TAI) 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 RISM

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 75% of the Italian MS centers have joined the RISM project.

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, 26 Research Assistants are active in 15 Italian Regions (following approximately 130 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 RISM project, 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.

EXECUTIVE COMMITTEE

Maria Trojano
University of Bari Aldo Moro, Department of Biomedicine Transnational and Neuroscience "DiBraiN" Multiple

Mario Alberto Battaglia
Italian Multiple Sclerosis Foundation, Genova

CURRENT SCIENTIFIC COMMITTEE AND ROLES

Maria Trojano, Chairman
University of Bari Aldo Moro, Department of Biomedicine Translational and Neuroscience "DiBraiN" Multiple Sclerosis Center, Bari

Mario Alberto Battaglia, Co-Chairman
Italian Multiple Sclerosis Foundation, Genova

Paola Mosconi, IRFMN Representative
Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano

Claudio Gasperini, Italian Neurological Society Representative
Department of Neurology, San Camillo-Forlanini Hospital, Rome

Eleonora Cocco, MS Clinical Centers Representative
Centro Sclerosi Multipla Ospedale Binaghi, Cagliari

Matilde Inglese, MS Clinical Centers Representative
Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa

Carla Tortorella, MS Clinical Centers Representative
Department of Neurosciences, S. Camillo-Forlanini Hospital, Rome

Marco Capobianco, Secretary
Centro Sclerosi Multipla, SC Neurologia, AO Santa Croce e Carle, Cuneo

Maria Pia Amato, Expert
Department of NEUROFARBA, University of Florence, Florence

Giancarlo Comi, Expert
Centro Sclerosi Multipla Casa di Cura Igea, Milano

Massimo Filippi, Expert
San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan

OBSERVATIONAL STUDIES EXPERT COMMITTEE

This committee is composed of neurologists (n=6) and statisticians (n=3) with the following responsibilities:

1) training activities designed for young neurologists who wish to enhance their skills in designing, conducting, and analysing observational studies on datasets extracted from RISM;
2) consultation activities for ongoing or upcoming studies.

A group of consultants with relevant expertise is called upon to collaborate with the 'Observational Studies Expert Committee'.

CURRENT OBSERVATIONAL STUDIES EXPERT COMMITTEE

Massimiliano Copetti (statistician)
Head of Unit of Biostatistics, I.R.C.C.S. Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Foggia, Italy

Giuseppe Lucisano (statistician)
Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari Aldo Moro, Bari, Italy

Claudia Santucci (statistician)
Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano

Diana Ferraro (neurologist)
Centro dell'Ospedale Civile di Baggiovara, Azienda Ospedaliero-Universitaria di Modena Sclerosi Multipla

Pietro Iaffaldano (neurologist)
University of Bari Aldo Moro, Department of Biomedicine Translational and Neuroscience "DiBraiN" Multiple Sclerosis Center, Bari

Lorena Lorefice (neurologist)
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Emilio Portaccio (neurologist)
Department of NEUROFARBA, University of Florence, Florence

Luca Prosperini (neurologist)
U.O.C. Neurologia e Neurofisiopatologia, A.O. S. Camillo-Forlanini, Roma

Maria Assunta Rocca (neurologist)
San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan

Consultants of the observational studies expert committee

Roberto Bergamaschi *(neurologist) Multiple Sclerosis Center, IRCCS Mondino Foundation*

Matteo Foschi *(neurologist) Dipartimento di Neuroscienze, Centro SM e Malattie Neurodegenerative - U.O.C. Neurologia,Ospedale S. Maria delle Croci, AUSL Romagna, Ravenna*

Giorgia Teresa Maniscalco *(neurologist) Centro Regionale di Diagnosi e Terapia della Sclerosi Multipla*

Elisabetta Signoriello *(neurologist) Centro Clinico per la Sclerosi Multipla - II Clinica Neurologica - II Università di Napoli*

TECHNICAL AND METHODOLOGICAL STRUCTURE

Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano

Coordination: *Paola Mosconi, Pasquale Paletta, Vito Lepore*

Development and support of the web platform: *Antonio D'Ettorre, Donatella Corrado, Lorenzo Rossi, Massimo Vitali, Andrea D'Amico, Lorenzo Marfisi*

Statistician: *Claudia Santucci*

Technical secretary: *Sabrina Bidoli*

TECHNICAL AND ADMINISTRATIVE INFRASTRUCTURE

Italian Multiple Sclerosis Foundation, Genova

Coordination: *Michela Ponzio*

Clinical study coordinator for PASS projects: *Marco Salivetto*

Research assistant network manager: *Alessia Elia*

Legal office: *Paolo Bandiera, Laura De Barbieri, Martina Bassi*

Technical secretary: *Luciana Lunadei, Maria Rita Di Fazio*

Director of scientific research at FISM: *Paola Zaratin*

RESEARCH ASSISTANTS NETWORK

Italian Multiple Sclerosis Foundation, Genova

Senior staff: *Beatrice Biolzi, Daniele Dell'Anna, Sonia Di Lemme, Chiara Di Tillio, Federica Martini, Ornella Moreggia, Ilaria Maietta, Ramona Piredda, Silvia Perugini, Chiara Raimondi, Antonino Rallo, Monica Romoli, Ilaria Rossi*

Junior staff: *Camilla Borgo, Antonella Carta, Paola Crida, Marco Delogu, Teresa Fonsdituri, Agata Marchese, Martina Marciano, Silvia Marinetto, Chiara Monetti, Ludovica Roselli, Valentina Tallarico, Stefania Treccarichi, Eliana Zaccone*

HIGHLIGHTS FROM 2022-2024

Annual Scientific Congresses of the Italian MS Society and its Foundation:

- **"Connecting MS with other neurodegenerative diseases: together we are stronger" | Rome, 26 May 2022**
- **"Pathways to cure", Session dedicated to RISM | Rome, 1 June 2023**
- **Brain health: rethinking the diagnosis of multiple sclerosis and related disorders, Session dedicated to RISM, Rome, 29 May 2024**

The Italian MS Society, through its Foundation, supports, with its own resources, research projects dedicated to specific areas of interest, and whose results are presented during the Annual Scientific Congress.

A session is dedicated to the completed projects that analysed data collected by RISM. The Congress also hosts an annual meeting of the staff involved in RISM, including members of the Technical Structure and Administrative Infrastructure and the network of research assistants. The meeting provides the opportunity to share the latest updates on the platform and addresses common issues regarding data collection, with the aim of improving the overall quality of RISM.

The Big Multiple Sclerosis Data Network meeting in Prague, 8-10 June 2022

The Big MS Data Network initiative brings together leading MS registries to conduct large observational studies using Real World Data. In June 2022, the first meeting in person of the Big MS Data Network since the start of the COVID-19 pandemic took place, while this year the meeting was organised in Copenaghen. The teams of Italian, French, Danish, Czech, Swedish registries, and of the international data sharing initiative MSBase, discussed on operational aspects such as the use of a common data model for federated analyses and future efforts to promote the initiative.

The Big Multiple Sclerosis Data Network meeting in Copenhagen, 12 May 2023

The Big MS Data Network met in May 2023 to discuss the topic: "BigMS – pharma PASS Forum". The meeting agenda included issues such as qualification opinion effort with EMA, the inclusion of new registries, and current and future collaborations concerning topics of interest such as the long-term safety evaluation of MS treatments, or the use of registries to support regulatory and HTA-decision making.

2nd BigMS Workshop "Statistical methods to address specific RWE questions", "Novel modelling approaches for RWD analysis" | Bari, 14-16 June 2023

During the 3-days workshop promoted by the BigMS Data Network, international experts discussed important topics related to how to make use of databases of Real World Data to generate reliable and useful results. The workshop agenda concerned the comparison between conventional statistical approaches versus machine learning methods about three main topics: predictive approaches to heterogeneous treatment effects in MS, comparative effectiveness and safety of DMTs' sequences in MS, and safety analysis using RWD.

The Big Multiple Sclerosis Data Network meeting in Belfast, 17 May 2024

The Big MS Data Network met in May 2024 to discuss the topic: "Handing over the coordination responsibility of the initiative" The meeting agenda included issues such as the update the BMSD Homepage; the organization of the next BMSD F2F 2025; the creation of BMSD working group; the inclusion of new registries, and current and future collaborations.

The Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)

- **The 38th ECTRIMS Congress in Amsterdam | 26-28 October 2022**
- **The 39th ECTRIMS Congress in Milan | 11-13 October 2023**
- **The 40th ECTRIMS Congress in Copenhagen | 18-20 September 2024 (upcoming)**

In recent years, data collection initiatives have received increasing attention at the ECTRIMS Congress, with the opportunity to share their newest insights and strengthen the network for international collaboration. Each year RISM attends the Congress with a stand to present the initiative and its objectives in the fields of public health and research.

RISM Annual Meeting of the Participating MS Clinical Centers

- **Milan | 06 December 2022**
- **Naples | 22 October 2023**
- **Rome | 9-12 November 2024 (upcoming, date to be defined)**

The neurologists of the Italian MS centers participating in RISM are all invited to join the Annual Meeting, where the latest updates and progress of the project are presented. At the 2024 Meeting in Rome the activity plan by the Observational Studies Expert Committee for 2025 will be presented.

DEDICATED SOFTWARE

During the first years, RISM 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, RISM is running on a new modular web-based software in an exclusive way, named the "RISM-App". Currently the software release is 3.3.9. The software access happens via the reserved area of the website of the project (*https://www.registroitalianosm.it/*).

CHARACTERISTICS 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.
- **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. A Privacy Impact Assessment has been made to assess the security level of the website.
- **Standardized:** the database uses standardized codings, such as MedDRA, ICD9CM, Eurocat and Farmadati. A Standard Operating Procedures manual is periodically updated to standardize data collection and RISM-App utilization.
- **Printable:** it is possible to print a report containing patient information.
- **Modular:** it is possible to add several modules.

SOFTWARE STRUCTURE OF RISM

The RISM 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 Therapies (AEs and SAEs are codified using MedDRA; Comorbidities are codified using ICD9CM).

MRI
This section is dedicated to conventional magnetic resonance imaging (MRI) measures (brain and spinal cord 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, etc...

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: Neuromyelitis Optica Spectrum Disorder (NMOSD) such as Neuromyelitis Optica 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 people with an MS pediatric-onset. 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 the 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 two 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:

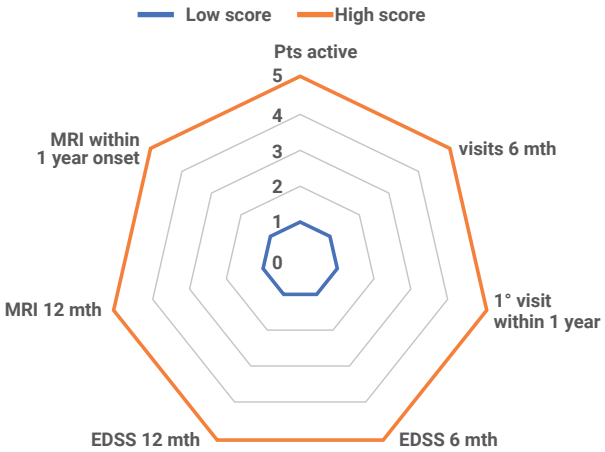
- **dates:** presence/absence, completeness, anomalies and consistency among all the data collected in the dataset
- **completeness:** overall evaluation of the completeness level of the variables included
- **accuracy:** proportion of variables with a value corresponding to their range
- **consistency:**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

Based on our previous published experience (2), an ad hoc working group was established and reviewed the previous set of indicators with the aim to improve the quality, completeness, timeliness, generalization, and representativeness of the collected data.
Accordingly, the following indicators were established:

- a set of seven performance indicators reported as radar graph; for each indicator all the centers were awarded with a score of 5 for the best performance, while lower scores of 4 to 1 were attributed for progressively lower performances.
- a set of four epidemiological-descriptive indicators:
  - female/male ratio,
  - distribution of patients with/without a DMT prescription,
  - distributions of age at onset, interval between onset date and diagnosis date, and interval between diagnosis date and first DMT start date,
  - frequencies of first and last DMT

Every six months, each PI and team receive a report where data and performance indicators of their own center are bench-marked with the whole sample: in this way, each center can assess its own performances and the level of improvement over the time.

Alongside with this work, a thorough assessment of data accuracy and consistency was carried out by identifying potential duplicates in the whole database (2,101 identified at September 2023) and checking them one by one, fixing the incongruencies and unifying the duplicates (726 left at July 2024).
Here the seven performance indicators and their graphical representation (radar graph):



1. ***Pts active:*** *at least 1 visit in the last 2 years*
2. ***Visits 6 mth:*** *at least 1 visit every 6 months*
3. ***1° visit within 1 year:*** *first visit within 12 months of disease onset*
4. ***EDSS 6 mth:*** *at least 1 EDSS evaluation every 6 months*
5. ***EDSS 12 mth:*** *at least 1 EDSS evaluation every 12 months*
6. ***MRI 12 mth:*** *At least 1 MRI (brain and spinal cord) every 12 months*
7. ***MRI within 1 year onset:*** *At least 1 MRI (brain and spinal cord) within 12 months of disease onset*

(2) Mosconi P, Guerra T, Paletta P, D'Ettorre A, Ponzio M, Battaglia MA, Amato MP, Bergamaschi R, Capobianco M, Comi G, Gasperini C, Patti F, Pugliatti M, Ulivelli M, Trojano M, Lepore V; Italian Multiple Sclerosis and Related Disorders Register Centres Group. Data monitoring roadmap. The experience of the Italian Multiple Sclerosis and Related Disorders Register. Neurol Sci. 2023 Jun; doi: 10.1007/s10072-023-06876-9.

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 co-morbidity on the effectiveness and safety of disease-modifying therapies. 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 RISM, has been recognized as a high quality initiative by EMA, able to provide data for PASS.
Currently, four PASS based on RISM 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)
4. Kesimpta long-term retrospective safety study utilizing realworld data from existing multiple sclerosis registries and databases from multiple countries (NOVARTIS)

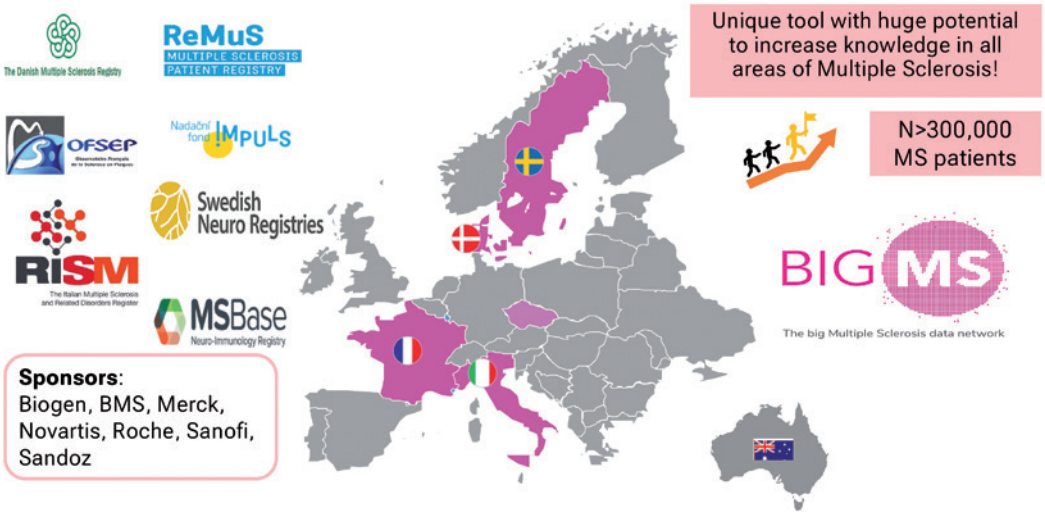
BIG MS DATA NETWORK

From January 2024, RISM will become responsible for the coordination of the BigMS Data Network. The Network will be coordinated jointly by RISM and the Karolinska Institutet until the end of 2024, to allow the gradual and practical transfer of the coordination tasks to the Italian MS Register staff.

General coordination tasks from 2024:
Chairman BMSD coordination: Maria Trojano, Professor of Neurology at University Aldo Moro Bari
Responsible of Organization: Prof. Mario Alberto Battaglia, Professor of Hygiene and Public Health, University of Siena, President of Italian MS Foundation
Project coordinator: Pietro Iaffaldano, Associated Professor of Neurology at University Aldo Moro Bari

Other staff:
University of Bari: **Giuseppe Lucisano,** *Msc, Statistician at CORESEARCH (Pescara, Italy) and at the University of Bari Aldo Moro*
Tommaso Guerra, *Neurologist at the University Aldo Moro Bari*

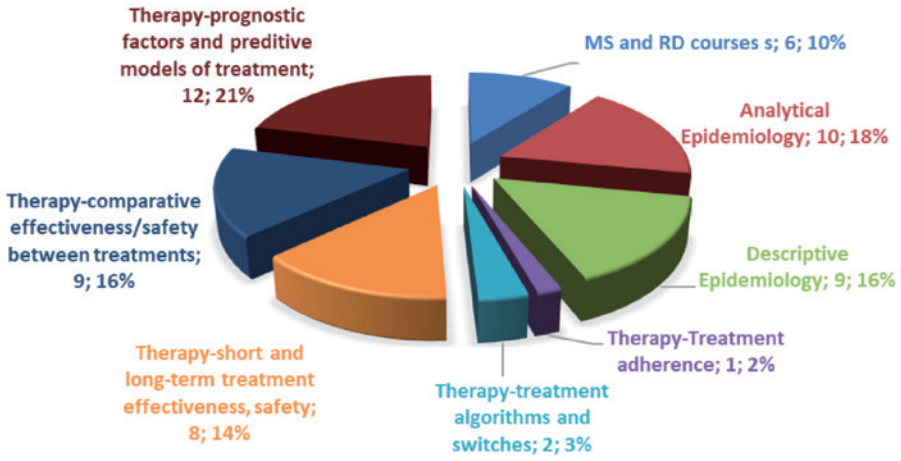
FISM: **Paola Zaratin,** *PhD Director of Scientific Research at FISM*
Michela Ponzio, *PhD Coordinator of Research in Epidemiology and Public Health*
Marco Salivetto, *Clinical Study Monitor for PASSs*
Paolo Bandiera, *General Affairs and Institutional Relations Director*



RESEARCH PROJECTS BASED ON THE RISM DATA

Currently 57 projects approved, 32 completed and 25 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, NMOSD 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)



Here are reported the title of 25 ongoing projects

Principal Investigator	*Title of the project*	*Priority areas*
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*
Emilio Portaccio	*Optimal responder alle terapie disease modifying "platform", in una coorte Italiana di pazienti con sclerosi multipla ad esordio recidivante remittente*	*Terapia – fattori prognostici e modelli predittivi di riposte al trattamento*
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*
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	*Evaluating the clinicAl and MRI characteristics of Secondary Progressive multiplE sclerosis; a registRy- bAsed/multicentric cohort study (ASPERA).*	*Analytical Epidemiology - prognostic factors*
Francesco Patti	*Clinical and neuroradiological findings in patients with late-onset multiple sclerosis (LOMS)*	*MS and RD courses - late onset*
Massimo Filippi	*Predictors of response to cladribine in multiple sclerosis patients*	*Therapy - prognostic factors and predictive models of treatment response*
Emilio Portaccio	*Optimal responders to platform disease modifying therapies in an Italian cohort of relapsing-onset multiple sclerosis patients*	*Therapy - prognostic factors and predictive models of treatment response*

Principal Investigator	Title of the project	Priority areas
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*
Massimo Filippi	*AFFectS – Anti-CD20 eFFectiveness and Safety profile in a large cohort of multiple sclerosis patients*	*Therapy - prognostic factors and predictive models of treatment response*
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*
Francesco Patti	*Evaluating the effectiveness of Rituximab in rElapsiNg Multiple Sclerosis patiEnts previously treated with hiGhly-Active Disease modifying thErapies (RENEGADE)*	*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*
Marta Simone	*Multi-centre, prospective/retrospective, randomised, open label pragmatic trial to compare the effectiveness and safety of interferon beta-1a (IFN beta-1a) administered weekly i.m. and glatiramer-acetate (GA) in pediatric patients affected by multiple sclerosis*	*Therapy - comparative effectiveness / safety between treatments*
Emilio Portaccio	*Comparative effectiveness of disease modifying treatments and Autologous Hematopoietic Stem Cell Transplant on the risk of first progression independent of relapse activity in relapsing multiple sclerosis*	*Therapy - comparative effectiveness / safety between treatments*
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 - late onset*
Ermelinda De Meo	*Phenotyping progression in multiple sclerosis*	*Therapy - prognostic factors and predictive models of treatment response*
Aurora Zanghì	*Fingolimod Exit strategy: a real word Italian registry study*	*Therapy - comparative effectiveness / safety between treatments*
Pietro Iaffaldano	*Characterization of non-active secondary progressive multiple sclerosis: diagnosis challenge ad assessment of progression independent from relapse activity phenomena*	*MS and RD courses - late onset*
Pietro Iaffaldano	*Assessment of cladribine therapy over time: effectiveness, safety and evaluation of treatment sequencing beyond year four*	*Therapy - prognostic factors and predictive models of treatment response*
Shalom Haggiag	*Comparative Effectiveness of Cladribine versus S1PR Modulators in Naive Patients with Relapsing-Remitting Multiple Sclerosis: An Observational Study*	*Descriptive Epidemiology - prevalence*
Eleonora Tavazzi	*The impact of sex/gender on epidemiology, access to health facilities and treatment approach in people with multiple sclerosis. Results from the Italian Multiple Sclerosis and Related Disorders Register*	*Descriptive Epidemiology - prevalence*

Italian Multiple Sclerosis and Related Disorders Register: the most relevant publications

A comparison of natalizumab and ocrelizumab on disease progression in multiple sclerosis

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Iaffaldano P, Lucisano G, Guerra T, Paolicelli D, Portaccio E, Inglese M, Foschi M, Patti F, Granella F, Romano S, Cavalla P, De Luca G, Gallo P, Bellantonio P, Gallo A, Montepietra S, Di Sapio A, Vianello M, Quatrale R, Spitaleri D, Clerici R, Torri Clerici V, Cocco E, Brescia Morra V, Marfia GA, Boccia VD, Filippi M, Amato MP, Trojano M; **Italian MS Register**. *A comparison of natalizumab and ocrelizumab on disease progression in multiple sclerosis*. **Ann Clin Transl Neurol. 2024** Jul. doi: 10.1002/acn3.52118.

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ABSTRACT

Objective No direct comparisons of the effect of natalizumab and ocrelizumab on progression independent of relapse activity (PIRA) and relapse-associated worsening (RAW) events are currently available. We aimed to compare the risk of achieving first 6 months confirmed PIRA and RAW events and irreversible Expanded Disability Status Scale (EDSS) 4.0 and 6.0 in a cohort of naïve patients treated with natalizumab or ocrelizumab from the Italian Multiple Sclerosis Register.

Methods Patients with a first visit within 1 year from onset, treated with natalizumab or ocrelizumab, and ≥3 visits were extracted. Pairwise propensity score-matched analyses were performed. Risk of reaching the first PIRA, RAW, and EDSS 4.0 and 6.0 events were estimated using multivariable Cox proportional hazards models. Kaplan-Meier curves were used to show cumulative probabilities of reaching outcomes.

Results In total, 770 subjects were included (natalizumab = 568; ocrelizumab = 212) and the propensity score-matching retrieved 195 pairs. No RAW events were found in natalizumab group and only 1 was reported in ocrelizumab group. A first PIRA event was reached by 23 natalizumab and 25 ocrelizumab exposed patients; 7 natalizumab- and 10 ocrelizumab-treated patients obtained an irreversible EDSS 4.0, while 13 natalizumab- and 15 ocrelizumab-treated patients reached an irreversible EDSS 6.0. No differences between the two groups were found in the risk (HR, 95%CI) of reaching a first PIRA (1.04, 0.59-1.84; p = 0.88) event, an irreversible EDSS 4.0 (1.23, 0.57-2.66; p = 0.60) and 6.0 (0.93, 0.32-2.68; p = 0.89).

Interpretation Both medications strongly suppress RAW events and, in the short term, the risk of achieving PIRA events, EDSS 4.0 and 6.0 milestones is not significantly different.

THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Early-aggressive treatment algorithm versus classical escalation therapy in relapsing Multiple Sclerosis

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Temporal and spatial patterns in the prescriptions of disease-modifying therapies for multiple sclerosis. Results from the Italian Multiple Sclerosis and Related Disorders Register

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Lepore V, Paletta P, Bosetti C, Santucci C, Ponzio M, Pupillo E, Leone MA, Bergamaschi R, Mosconi P, **Italian Multiple Sclerosis and Related Disorders Register Centers Group and the Scientific Committee of the Italian Multiple Sclerosis and Related Disorders** *Temporal and spatial patterns in the prescriptions of disease-modifying therapies for multiple sclerosis. Results from the* **Italian Multiple Sclerosis and Related Disorders Register. Mult Scler Relat Disord. 2024** Jul;87:105638. doi: 10.1016/j.msard.2024.105638.

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ABSTRACT

Background The therapeutic scenario in multiple sclerosis (MS) has evolved over recent years with the progressive introduction of new drugs focused to better balance efficacy, safety and management requirements. The objective of this study was to examine the prescribing patterns of disease-modifying therapies (DMT) over time and across different geographic areas, and the latency between disease onset, first Register center visit, disease diagnosis, and the start of treatment in a large cohort of persons with MS from the Italian Multiple Sclerosis and Related Disorders Register.

Methods Up to 2022, the Register collected data from 124 centers on more than 78,000 persons, of whom 56,872 received at least one DMT prescription. Beside baseline demographic and clinical characteristics, we focused on DMT according to their efficacy distinguishing between moderate-efficacy (ME), or high-efficacy (HE).

Results There was a higher probability of prescribing HE-DMT for increasing calendar years (multivariable odds ratio, OR=11.51 in 2021 or thereafter vs before 2000), in males (OR=1.08 vs females), patients with primary progressive with or without relapse (OR=3.00 vs clinically isolated syndrome), those with a higher Expanded Disability Status Scale score (OR=3.85 for >4 versus 0-1), and those from larger referral centers (OR=1.89 vs smaller ones). Conversely, higher age at onset was associated to a lower probability of prescribing HE-DMT (OR=0.74 at 40 or

more vs <20 years). A trend to shorter times was observed in subsequent calendar years for disease onset, first center visit, diagnosis and first DMT prescription. No trend was detected based on the location of the geographic referral centers. The times between disease onset, first center visit, and diagnosis and the first DMT prescription showed significant decreases according to the year, while differences were less evident for the geographic areas.

Conclusion This study highlights some factors influencing the choice of HE-DMT, including aspects of both across different Italian MS centers.

DESCRIPTIVE EPIDEMIOLOGY

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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

PRINCIPAL INVESTIGATOR

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Big Multiple Sclerosis Data network: an international registry research network

REFERENCE
Glaser A, Butzkueven H, van der Walt A, Gray O, Spelman T, Zhu C, Trojano M, Iaffaldano P, Battaglia MA, Lucisano G, Vukusic S, Vukusic I, Casey R, Horakova D, Drahota J, Magyari M, Joensen H, Pontieri L, Elberling F, Klyve P, Mouresan EF, Forsberg L, Hillert J. *Big Multiple Sclerosis Data network: an international registry research network.* **J Neurol. 2024** Jun;271(6):3616-3624. doi: 10.1007/s00415-024-12303-6.

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ABSTRACT

Background The Big Multiple Sclerosis Data (BMSD) network (https://bigmsdata.org) was initiated in 2014 and includes the national multiple sclerosis (MS) registries of the Czech Republic, Denmark, France, Italy, and Sweden as well as the international MSBase registry. BMSD has addressed the ethical, legal, technical, and governance-related challenges for data sharing and so far, published three scientific papers on pooled datasets as proof of concept for its collaborative design.

Data collection Although BMSD registries operate independently on different platforms, similarities in variables, definitions and data structure allow joint analysis of data. Certain coordinated modifications in how the registries collect adverse event data have been implemented after BMSD consensus decisions, showing the ability to develop together.

Data management Scientific projects can be proposed by external sponsors via the coordinating centre and each registry decides independently on participation, respecting

its governance structure. Research datasets are established in a project-to-project fashion and a project-specific data model is developed, based on a unifying core data model. To overcome challenges in data sharing, BMSD has developed procedures for federated data analysis.

Future perspectives Presently, BMSD is seeking a qualification opinion from the European Medicines Agency (EMA) to conduct post-authorization safety studies (PASS) and aims to pursue a qualification opinion also for post-authorization effectiveness studies (PAES). BMSD aspires to promote the advancement of real-world evidence research in the MS field.

THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Big Multiple Sclerosis Data (BMSD) Network

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COLLABORATIONS WITH OTHER CENTERS

All the PI of all the MS centers participating to the Italian MS Registry

Long-term effectiveness of natalizumab in secondary progressive multiple sclerosis: a propensity-matched study

REFERENCE
Chisari CG, Aguglia U, Amato MP, Bergamaschi R, Bertolotto A, Bonavita S, Morra VB, Cavalla P, Cocco E, Conte A, Cottone S, De Luca G, Di Sapio A, Filippi M, Gallo A, Gasperini C, Granella F, Lus G, Maimone D, Maniscalco GT, Marfia G, Moiola L, Paolicelli D, Pesci I, Ragonese P, Rovaris M, Salemi G, Solaro C, Totaro R, Trojano M, Vianello M, Zaffaroni M, Lepore V, Patti F; **Italian MS Register Study Group**. Long-term effectiveness of natalizumab in secondary progressive multiple sclerosis: A propensity-matched study. **Neurotherapeutics. 2024** May;21(4):e00363. doi: 10.1016/j.neurot.2024.e00363.

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ABSTRACT

Treatment options for secondary progressive MS (SPMS) are limited, especially considering that the new drugs recently approved are licensed for actively relapsing patients. We aimed to compare the disability progression in a real-world cohort of SPMS patients treated with natalizumab (NTZ) or interferon beta-1b (IFNb-1b). This multicenter retrospective enrolled patients with a diagnosis of SPMS according to 2014 Lublin criteria, who received NTZ or IFNb-1b for at least 48 months between the 1st June 2012 and the 15th May 2018 at 33 Italian MS centers contributing to the Italian MS Registry NTZ or IFNb-1b. Confirmed Expanded Disability Status Scale worsening (CEW) and progression independent of relapse (PIRA) were evaluated. In order to correct for non-randomization, a propensity score matching of the groups was performed. Out of 5206 MS patients identified at the time of data extraction, 421 SPMS patients treated with NTZ (224 [53.2%] females, mean age 45.3 ± 25.4 years) and 353 with IFNb-1b (133 [37.8%] females, mean age 48.5 ± 19.8 years) were enrolled. After applying the matching procedure, 102 patients were retained in the NTZ group and 98 in the IFNb-2b group. The proportion of patients who reached the 48-month 1-point CEW was significantly higher in IFNb-1b compared to NTZ group (58.2% versus 30.4%, p = 0.01). The proportion of patients who developed PIRA at 48 months were significantly higher in IFNb-1b compared to NTZ (72.4% versus 40.2%, p = 0.01). EDSS before treatment initiation and SPMS duration were risk factors for disability progression in terms of PIRA (HR 2.54, 25%CI 1.67-5.7; p = 0.006 and HR 2.04, 25%CI 1.22-3.35; p = 0.01, respectively). Patients treated with IFNb-1b were 1.64 times more to likely to develop PIRA (HR 1.64, 25%CI 1.04-4.87; p = 0.001). Treatment with NTZ in SPMS patients showed more favorable disability outcomes compared to IFNb-1b with beneficial effects over 48 months.

THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Comparative effectiveness of different Natalizumab dosing schedules in real world life: a retrospective Italian multicentre study

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Progression independent of relapse activity in relapsing multiple sclerosis: impact and relationship with secondary progression

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ABSTRACT

Objectives We investigated the occurrence and relative contribution of relapse-associated worsening (RAW) and progression independent of relapse activity (PIRA) to confirmed disability accrual (CDA) and transition to secondary progression (SP) in relapsing multiple sclerosis (MS).

Methods Relapsing-onset MS patients with follow-up > / = 5 years (16,130) were extracted from the Italian MS Registry. CDA was a 6-month confirmed increase in Expanded Disability Status Scale (EDSS) score. Sustained disability accumulation (SDA) was a CDA with no EDSS improvement in all subsequent visits. Predictors of PIRA and RAW and the association between final EDSS score and type of CDA were assessed using logistic multivariable regression and multivariable ordinal regression models, respectively.

Results Over 11.8 ± 5.4 years, 16,731 CDA events occurred in 8998 (55.8%) patients. PIRA (12,175) accounted for 72.3% of CDA. SDA occurred in 8912 (73.2%) PIRA and 2583 (56.7%) RAW ($p < 0.001$). 4453 (27.6%) patients transitioned to SPMS, 4010 (73.2%) out of 5476 patients with sustained PIRA and 443 (24.8%) out of 1790 patients with non-sustained PIRA. In the multivariable ordinal regression analysis, higher final EDSS score was associated with PIRA (estimated coefficient 0.349, 95% CI 0.120-0.577, $p = 0.003$).

Discussion In this real-world relapsing-onset MS cohort, PIRA was the main driver of disability accumulation and was associated with higher disability in the long term. Sustained PIRA was linked to transition to SP and could represent a more accurate PIRA definition and a criterion to mark the putative onset of the progressive phase.

THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Towards a unified definition of progression independent of relapse activity in relapsing multiple sclerosis

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Disease-modifying therapies in managing disability worsening in paediatric-onset multiple sclerosis: a longitudinal analysis of global and national registries

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ABSTRACT

Background High-efficacy disease-modifying therapies have been proven to slow disability accrual in adults with relapsing-remitting multiple sclerosis. However, their impact on disability worsening in paediatric-onset multiple sclerosis, particularly during the early phases, is not well understood. We evaluated how high-efficacy therapies influence transitions across five disability states, ranging from minimal disability to gait impairment and secondary progressive multiple sclerosis, in people with paediatric-onset multiple sclerosis.

Methods Longitudinal data were obtained from the international MSBase registry, containing data from people with multiple sclerosis from 151 centres across 41 countries, and the Italian Multiple Sclerosis and Related Disorders Register, containing data from people with multiple sclerosis from 178 Italian multiple sclerosis centres. People younger than 18 years at the onset of multiple sclerosis symptoms were included, provided they had a confirmed diagnosis of relapsing-remitting multiple sclerosis and at least four Expanded Disability Status Scale (EDSS) scores recorded within 12-month intervals. The primary outcome was the time to change in disability state: minimal disability (EDSS scores 0, 1·0, and 1·5), mild disability (EDSS scores 2·0 and 2·5), moderate disability (EDSS scores 3·0 and 3·5), gait impairment (EDSS scores ≥4·0), and clinician diagnosed secondary progressive multiple sclerosis. A multi-state model was constructed to simulate the natural course of multiple sclerosis, modelling the probabilities of both disability worsening and improvement simultaneously. The impact of high-efficacy disease-modifying therapies (alemtuzumab, cladribine, daclizumab, fingolimod, mitoxantrone, natalizumab, ocrelizumab, rituximab, or autologous haematopoietic stem cell transplantation) and low-efficacy disease-modifying therapies (dimethyl fumarate, glatiramer acetate, interferon beta, or teriflunomide), compared with no treatment, on the course of disability was assessed. Apart from recruitment, individuals with lived experience of multiple sclerosis were not involved in the design and conduct of this study.

Findings A total of 5224 people (3686 [70·6%] female and 1538 [29·4%] male) with mean age at onset of multiple sclerosis 15·24 years (SD 2·52) were included. High-efficacy therapies reduced the hazard of disability worsening across the disability states. The largest reduction (hazard ratio 0·41 [95% CI 0·31-0·53]) was observed in participants who were treated with high-efficacy therapies while in the minimal disability state, compared with those remained untreated. The benefit of high-efficacy therapies declined with increasing disability. Young people with minimal disability who received low-efficacy therapy also experienced a reduced hazard (hazard ratio 0·65 [95% CI 0·54-0·77]) of transitioning to mild disability, in contrast to those who remained untreated.

Interpretation Treatment of paediatric-onset relapsing-remitting multiple sclerosis with high-efficacy therapy substantially reduces the risk of reaching key disability milestones. This reduction in risk is most pronounced among young people with minimal or mild disability when treatment began. Children with relapsing-remitting multiple sclerosis should be treated early with high-efficacy therapy, before developing significant neurological impairments, to better preserve their neurological capacity.

THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Timing and comparative effectiveness of high-efficacy disease-modifying therapies in childhood-onset multiple sclerosis

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Late-onset multiple sclerosis: disability trajectories in relapsing-remitting patients of the Italian MS Registry

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ABSTRACT

Background Generally infrequent, multiple sclerosis (MS) with late onset (LOMS) is characterized by an onset over the age of 50 and a mainly progressive course, while relapsing–remitting (RR) forms are less frequently observed and explored. This study aimed to characterize a large cohort of MS patients with RRMS at onset to assess the baseline factors related to the worst disability trajectories and explore the role of LOMS.

Methods The data were extracted from the Italian MS Register (IMSR). Disability trajectories, defined using at least two and up to twenty expanded disability status scale (EDSS) assessments annually performed, were implemented using group-based trajectory models (GBTMs) to identify different groups with the same trajectories over time. MS profiles were explored using multinomial logistic regression.

Results A total of 16,159 RR patients [1012 (6.26%) presented with LOMS] were analyzed. The GBTM identified four disability trajectories. The group with the most severe EDSS trend included 12.3% of the patients with a mean EDSS score>4, which increased over time and exceeded 6 score. The group with medium severity EDSS trend comprised 21.9% of the patients and showed a change in EDSS>3 scores over time. The largest group with 50.8% of patients reported a constant EDSS of 2 score. Finally, the benign group comprised 14.9% of the patients with a low and constant EDSS of 1 score over time. The probability of being in the worst groups increased if the patient was male; had LOMS or experienced brainstem, spinal, or supratentorial symptoms.

Conclusions Four MS severity profiles among RRMS patients in the IMSR have been reported, with LOMS being associated with a rapid worsening of EDSS scores. These findings have important implications for recognizing and managing how older age, aging, and age-related factors interact with MS and its evolution.

DESCRIPTIVE EPIDEMIOLOGY

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Clinical characteristics and disease outcomes of late onset Multiple Sclerosis: a retrospective multicenter study

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Evaluation of drivers of treatment switch in relapsing multiple sclerosis: a study from the Italian MS Registry

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ABSTRACT

Background Active relapsing-remitting (RR) and secondary progressive (SP) multiple sclerosis (MS) are currently defined as "relapsing MS" (RMS). The aim of this cross-sectional study was to assess drivers of treatment switches due to clinical relapses in a population of RMS patients collected in the Italian MS and Related Disorders Register (I-MS&RD).

Methods RRMS and SPMS patients with at least one relapse in a time window of 2 years before of data extraction were defined as RMS. Factors associated with disease-modifying therapy (DMT) switching due to clinical activity were assessed through multivariable logistic regression models in which treatment exposure was included as the last recorded DMT and the last DMT's class [moderate-efficacy (ME), high-efficacy (HE) DMTs and anti-CD20 drugs].

Results A cohort of 4739 RMS patients (4161 RRMS, 578 SPMS) was extracted from the I-MS&RD. A total of 2694 patients switching DMTs due to relapses were identified. Switchers were significantly ($p < 0.0001$) younger, less disabled, more frequently affected by an RR disease course in comparison to non-switcher patients. The multivariable logistic regression models showed that Alemtuzumab (OR 0.08, 95% CI 0.02-0.37), Natalizumab (0.48, 0.30-0.76), Ocrelizumab (0.1, 0.02-0.45) and Rituximab (0.23, 0.06-0.82) exposure was a protective factor against treatment switch due to relapses. Moreover, the use of HE DMTs (0.43, 0.31-0.59), especially anti-CD20 drugs (0.14, 0.05-0.37), resulted to be a protective factor against treatment switch due to relapses in comparison with ME DMTs.

Conclusions More than 50% of RMS switched therapy due to disease activity. HE DMTs, especially anti-CD20 drugs, significantly reduce the risk of treatment switch.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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

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Predictors of treatment switching in the Big Multiple Sclerosis Data Network

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ABSTRACT

Background Treatment switching is a common challenge and opportunity in real-world clinical practice. Increasing diversity in disease-modifying treatments (DMTs) has generated interest in the identification of reliable and robust predictors of treatment switching across different countries, DMTs, and time periods.

Objective The objective of this retrospective, observational study was to identify independent predictors of treatment switching in a population of relapsing-remitting MS (RRMS) patients in the Big Multiple Sclerosis Data Network of national clinical registries, including the Italian MS registry, the OFSEP of France, the Danish MS registry, the Swedish national MS registry, and the international MSBase Registry.

Methods In this cohort study, we merged information on 269,822 treatment episodes in 110,326 patients from 1997 to 2018 from five clinical registries. Patients were included in the final pooled analysis set if they had initiated at least one DMT during the relapsing-remitting MS (RRMS) stage. Patients not diagnosed with RRMS or RRMS patients not initiating DMT therapy during the RRMS phase were excluded from the analysis. The primary study outcome was treatment switching. A multilevel mixed-effects shared frailty time-to-event model was used to identify independent predictors of treatment switching. The contributing MS registry was included in the pooled analysis as a random effect.

Results Every one-point increase in the Expanded Disability Status Scale (EDSS) score at treatment start was associated with 1.08 times the rate of subsequent switching, adjusting for age, sex, and calendar year (adjusted hazard ratio [aHR] 1.08; 95% CI 1.07-1.08). Women were associated with 1.11 times the rate of switching relative to men (95% CI 1.08-1.14), whilst older age was also associated with an increased rate of treatment switching. DMTs star-

ted between 2007 and 2012 were associated with 2.48 times the rate of switching relative to DMTs that began between 1996 and 2006 (aHR 2.48; 95% CI 2.48-2.56). DMTs started from 2013 onwards were more likely to switch relative to the earlier treatment epoch (aHR 8.09; 95% CI 7.79-8.41; reference = 1996-2006).

Conclusion Switching between DMTs is associated with female sex, age, and disability at baseline and has increased in frequency considerably in recent years as more treatment options have become available. Consideration of a patient's individual risk and tolerance profile needs to be taken into account when selecting the most appropriate switch therapy from an expanding array of treatment choices.

THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Big Multiple Sclerosis Data (BMSD) Network

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Multiple Sclerosis Progression and Relapse Activity in Children

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ABSTRACT

Importance Although up to 20% of patients with multiple sclerosis (MS) experience onset before 18 years of age, it has been suggested that people with pediatric-onset MS (POMS) are protected against disability because of greater capacity for repair.

Objective To assess the incidence of and factors associated with progression independent of relapse activity (PIRA) and relapse-associated worsening (RAW) in POMS compared with typical adult-onset MS (AOMS) and late-onset MS (LOMS).

Design, Setting, and Participants IThis cohort study on prospectively acquired data from the Italian MS Register was performed from June 1, 2000, to September 30, 2021. At the time of data extraction, longitudinal data from 73 564 patients from 120 MS centers were available in the register.

Main Outcomes and Measures The main outcomes included age-related cumulative incidence and adjusted hazard ratios (HRs) for PIRA and RAW and associated factors.

Exposures Clinical and magnetic resonance imaging features, time receiving disease-modifying therapy (DMT), and time to first DMT.

Results After applying the inclusion and exclusion criteria, the study assessed 16 130 patients with MS (median [IQR] age at onset, 28.7 [22.8-36.2 years]; 68.3% female). Compared with AOMS and LOMS, patients with POMS had less disability, exhibited more active disease, and were exposed to DMT for a longer period. A first 48-week-confirmed PIRA occurred in 7176 patients (44.5%): 558 patients with POMS (40.4%), 6258 patients with AOMS (44.3%), and 360 patients with LOMS (56.8%) (P < .001). Factors associated with PIRA were older age at onset (AOMS vs POMS HR, 1.42; 95% CI, 1.30-1.55; LOMS vs POMS HR, 2.98; 95% CI, 2.60-3.41; P < .001), longer disease duration (HR, 1.04; 95% CI, 1.04-1.05; P < .001), and shorter DMT exposure (HR, 0.69; 95% CI, 0.64-0.74; P < .001). The incidence of PIRA was 1.3% at 20 years of age, but it rapidly increased approximately 7 times between 21 and 30 years of age (9.0%) and nearly doubled for each age decade from 40 to 70 years (21.6% at 40 years, 39.0% at 50 years, 61.0% at 60 years, and 78.7% at 70 years). The cumulative incidence of RAW events followed a similar trend from 20 to 60 years (0.5% at 20 years, 3.5% at 30 years, 7.8% at 40 years, 14.4% at 50 years, and 24.1% at 60 years); no further increase was found at 70 years (27.7%). Delayed DMT initiation was associated with higher risk of PIRA (HR, 1.16; 95% CI, 1.00-1.34; P = .04) and RAW (HR, 1.75; 95% CI, 1.28-2.39; P = .001).

Conclusions and Relevance PIRA can occur at any age, and although pediatric onset is not fully protective against progression, this study's findings suggest that patients with pediatric onset are less likely to exhibit PIRA over a decade of follow-up. However, these data also reinforce the benefit for DMT initiation in patients with POMS, as treatment was associated with reduced occurrence of both PIRA and RAW regardless of age at onset.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

INSPIRA - Italian analysis of the National multiple sclerosis registry Studying the concept of Progression Independent from Relapse Activity

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COVID-19 outbreak in Italy: an opportunity to evaluate extended interval dosing of ocrelizumab in MS patients

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ABSTRACT

Introduction During the COVID-19 pandemic, ocrelizumab (OCR) infusions for MS patients were often re-scheduled because of MS center's disruption and concerns regarding immunosuppression. The aim of the present study was to assess changes in OCR schedule during the first wave of pandemic in Italy and to evaluate the effect of delayed infusion on clinical/radiological endpoints.

Methods Data were extracted from the Italian MS Register database. Standard interval dosing was defined as an infusion interval ≤30 weeks, while extended interval dosing was defined as an infusion interval >30 weeks at the time of the observation period. Clinico-demographics variables were tested as potential predictors for treatment delay. Time to first relapse and time to first MRI event were evaluated. Cumulative hazard curves were reported along their 95% confidence intervals. A final sample of one-thousand two patients with MS from 65 centers was included in the analysis: 599 pwMS were selected to

evaluate the modification of OCR infusion intervals, while 717 pwRMS were selected to analyze the effect of infusion delay on clinical/MRI activity.

Results Mean interval between two OCR infusions was 28.1 weeks before pandemic compared to 30.8 weeks during the observation period, with a mean delay of 2.74 weeks (p<0,001). No clinico-demographic factors emerged as predictors of infusion postponement, except for location of MS centers in the North of Italy. Clinical relapses (4 in SID, 0 in EID) and 17 MRI activity reports (4 in SID, 13 in EID) were recorded during follow-up period.

Discussion Despite the significant extension of OCR infusion interval during the first wave of pandemic in Italy, a very small incidence of clinical/radiological events was observed, thus suggesting durable efficacy of OCR, as well as the absence of rebound after its short-term suspension.

THERAPY – TREATMENT ADHERENCE

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

OCREVID Study (The management of OCRElizumab during the coVID-19 pandemic in Italy)

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Effectiveness of Ocrelizumab in Primary Progressive Multiple Sclerosis: a Multicenter, Retrospective, Real world Study (OPPORTUNITY)

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ABSTRACT

Ocrelizumab is a recombinant humanized monoclonal antibody selectively targeting CD20-expressing B cells. The effect of ocrelizumab on primary progressive multiple sclerosis (PPMS) has been evaluated during phase 3 trials that enrolled patients under 55 years with a maximum Expanded Disability Status Scale (EDSS) of 6.5. However, little is known on older disabled patients with longer disease duration. We aimed to assess the clinical effectiveness of ocrelizumab in PPMS patients out of the ORATORIO eligibility criteria. This multicenter retrospective study collected data about the effectiveness of ocrelizumab in PPMS patients who received treatment between May 2017 and June 2022 in the Italian MS centers contributing to the Italian MS Registry who adhered to the Compassionate Use Program. The confirmed EDSS worsening (CEW) (defined as either a≥1-point or≥2-point increase in EDSS score from baseline that was confirmed at T12 and T24) was calculated. At the date of data extraction, out of 887 PPMS patients who had received ocrelizumab, 589 (mean age 49.7±10.7 years, 242 (41.1%) females) were enrolled. The mean follow-up period was 41.3±12.3 months. A total of 149 (25.3%) received ocrelizumab according to the ORATORIO criteria (ORATORIO group) and 440 (74.7%) outside the ORATORIO criteria (non-ORATORIO group). No differences in terms of cumulative probabilities of 12 and 24 months of CEW of≤1 point were found between ORATORIO and non-ORATORIO groups. Cox regression analyses showed that age older than 65 years (HR 2.51, 25% CI 1.07–3.65; p=0.01) was associated with higher risk of CEW at 24 months. Patients not responding to ORATORIO criteria for reimbursability may benefit from ocrelizumab treatment, as disease activity, disease duration, and EDSS seem to not impact the disability outcome. Our results may suggest to extend the possible use of this powerful agent in selected patients under the age of 65 years.

THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Evaluating the efficacy of Ocrelizumab in Primary PrOgRessive mulTiple sclerosis: a mUlticeNter retrospectIve sTudY (OPPORTUNITY)

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Data monitoring roadmap. The experience of the Italian Multiple Sclerosis and Related Disorders Register

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ABSTRACT

Introduction Over the years, disease registers have been increasingly considered a source of reliable and valuable population studies. However, the validity and reliability of data from registers may be limited by missing data, selection bias or data quality not adequately evaluated or checked. This study reports the analysis of the consistency and completeness of the data in the Italian Multiple Sclerosis and Related Disorders Register.

Methods The Register collects, through a standardized Web-based Application, unique patients. Data are exported bimonthly and evaluated to assess the updating and completeness, and to check the quality and consistency. Eight clinical indicators are evaluated.

Results The Register counts 77,628 patients registered by 126 centres. The number of centres has increased over time, as their capacity to collect patients. The percentages of updated patients (with at least one visit in the last 24 months) have increased from 33% (enrolment period 2000–2015) to 60% (enrolment period 2016–2022). In the cohort of patients registered after 2016, there were ≥ 75% updated patients in 30% of the small centres (33), in 9% of the medium centres (11), and in all the large centres (2). Clinical indicators show significant improvement for the active patients, expanded disability status scale every 6 months or once every 12 months, visits every 6 months, first visit within 1 year and MRI every 12 months.

Conclusions Data from disease registers provide guidance for evidence-based health policies and research, so methods and strategies ensuring their quality and reliability are crucial and have several potential applications.

Relapse-associated worsening in a real-life multiple sclerosis cohort: the role of age and pyramidal phenotype

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Zanghì A, Galgani S, Bellantonio P, Zaffaroni M, Borriello G, Inglese M, Romano S, Conte A, Patti F, Trojano M, Avolio C, D'Amico E; **Italian MS Registry.** *Relapse-associated worsening in a real-life multiple sclerosis cohort: the role of age and pyramidal phenotype.* **Eur J Neurol. 2023** Sep;30(9):2736-2744. doi: 10.1111/ene.15910.

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ABSTRACT

Background and purpose The overall disability in patients with relapsing–remitting multiple sclerosis is likely to be partly rather than entirely attributed to relapse.

Materials and methods The aim was to investigate the determinants of recovery from first relapse and relapse-associated worsening (RAW) in relapsing–remitting multiple sclerosis patients from the Italian MS Registry during a 5- year epoch from the beginning of first-line disease-modifying therapy. To determine recovery, the functional system (FS) score was used to calculate the difference between the score on the date of maximum improvement and the score before the onset of relapse. Incomplete recovery was defined as a combination of partial (1 point in one FS) and poor recovery (2 points in one FS or 1point in two FSs or any other higher combination). RAW was indicated by a confirmed dis-ability accumulation measured by the Expanded Disability Status Scale score confirmed6 months after the first relapse.

Results A total of 767 patients had at least one relapse within 5 years of therapy. Of these patients, 57.8% experienced incomplete recovery. Age (odds ratio [OR] 1.02, 95% confidence interval [CI] 1.01–1.04; p = 0.007) and pyramidal phenotype were associated within complete recovery (OR = 2.1, 95% CI 1.41–3.14; p < 0.001). RAW was recorded in 179(23.3%) patients. Age (OR = 1.02, 95% CI 1.01–1.04; p = 0.029) and pyramidal phenotype (OR = 1.84, 95% CI 1.18–2.88; p = 0.007) were the strongest predictors in the multivariable model.

Conclusions Age and pyramidal phenotype were the strongest determinants of RAW in early disease epochs.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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

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Hematopoietic Stem Cell Transplantation in People With Active Secondary Progressive Multiple Sclerosis

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ABSTRACT

Background and objectives Uncontrolled evidence suggests that autologous hematopoietic stem cell transplantation (AHSCT) can be effective in people with active secondary progressive multiple sclerosis (SPMS). In this study, we compared the effect of AHSCT with that of other anti-inflammatory disease-modifying therapies (DMTs) 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-month 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. Time to first CDP was assessed by means of proportional hazard Cox regression models. A linear mixed model with a time × treatment group interaction was used to assess the longitudinal EDSS time trends. Prevalence of improvement was estimated using a modified Kaplan-Meier estimator and compared between groups by bootstrapping the area under the curve.

Results Seventy-nine AHSCT-treated patients and 1975 patients treated with other DMTs (beta interferons, azathioprine, glatiramer-acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, and alemtuzumab) were matched to reduce treatment selection bias using propensity score and overlap weighting approaches. Time to first CDP was significantly longer in transplanted patients (hazard ratio [HR] = 0.50; 95% CI = 0.31-0.81; p = 0.005), with 61.7% of transplanted patients free from CPD at 5 years. Accordingly, EDSS time trend over 10 years was higher in patients treated with other DMTs than in AHSCT-treated patients (+0.157 EDSS points per year compared with -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 vs 4.6% of patients treated by other DMTs (p < 0.001).

Discussion 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 with standard immunotherapy.

Classification of evidence This study provides Class III evidence that autologous hematopoietic stem cell transplants prolonged the time to CDP compared with other DMTs.

THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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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Heterogeneity on long-term disability trajectories in patients with secondary progressive MS: a latent class analysis from Big MS Data network

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ABSTRACT

Background Over the decades, several natural history studies on patients with primary (PPMS) or secondary progressive multiple sclerosis (SPMS) were reported from international registries. In PPMS, a consistent heterogeneity on long-term disability trajectories was demonstrated. The aim of this study was to identify subgroups of patients with SPMS with similar longitudinal trajectories of disability over time.

Methods All patients with MS collected within Big MS registries who received an SPMS diagnosis from physicians (cohort 1) or satisfied the Lorscheider criteria (cohort 2) were considered. Longitudinal Expanded Disability Status Scale (EDSS) scores were modelled by a latent class growth analysis (LCGA), using a non-linear function of time from the first EDSS visit in the range 3-4.

Results A total of 3613 patients with SPMS were included in the cohort 1. LCGA detected three different subgroups of patients with a mild (n=1297; 35.9%), a moderate (n=1936; 53.6%) and a severe (n=380; 10.5%) disability trajectory. Median time to EDSS 6 was 12.1, 5.0 and 1.7 years, for the three groups, respectively; the probability to reach EDSS 6 at 8 years was 14.4%, 78.4% and 98.3%, respectively. Similar results were found among 7613 patients satisfying the Lorscheider criteria.

Conclusions Contrary to previous interpretations, patients with SPMS progress at greatly different rates. Our identification of distinct trajectories can guide better patient selection in future phase 3 SPMS clinical trials. Additionally, distinct trajectories could reflect heterogeneous pathological mechanisms of progression.

THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Big Multiple Sclerosis Data (BMSD) Network

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Towards a validated definition of the clinical transition to secondary progressive multiple sclerosis: A study from the Italian MS Register

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ABSTRACT

Background Definitions for reliable identification of transition from relapsing-remitting multiple sclerosis (MS) to secondary progressive (SP)MS in clinical cohorts are not available.

Objectives To compare diagnostic performances of two different data-driven SPMS definitions.

Methods Data-driven SPMS definitions based on a version of Lorscheider's algorithm (DDA) and on the EXPAND trial inclusion criteria were compared, using the neurologist's definition (ND) as gold standard, in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), Akaike information criterion (AIC) and area under the curve (AUC).

Results A cohort of 10,240 MS patients with ≥5 years of follow-up was extracted from the Italian MS Registry; 880 (8.5%) patients were classified as SPMS according to the neurologist definition, 1806 (17.6%) applying the DDA and 1134 (11.0%) with the EXPAND definition. The DDA showed greater discrimination power (AUC: 0.8 vs 0.6) and a higher sensitivity (77.1% vs 38.0%) than the EXPAND definition, with similar specificity (88.0% vs 91.5%). PPV and NPV were higher using the DDA than considering EXPAND definition (37.5% vs 29.5%; 97.6% vs 94.0%).

Conclusion Data-driven definitions demonstrated greater ability to capture SP transition than neurologist's definition and the global accuracy of DDA seems to be higher than the EXPAND definition.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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

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Disease-Modifying Treatments and Time to Loss of Ambulatory Function in Patients With Primary Progressive Multiple Sclerosis

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ABSTRACT

Importance Except for ocrelizumab, treatment options in primary progressive multiple sclerosis (PPMS) are lacking.

Objective To investigate the effectiveness of DMTs on the risk of becoming wheelchair dependent in a real-world population of patients with PPMS.

Design, setting, and participants This was a multicenter, observational, retrospective, comparative effectiveness research study. Data were extracted on November 28, 2018, from the Italian multiple sclerosis register and analyzed from June to December 2021. Mean study follow-up was 11 years. Included in the study cohort were patients with a diagnosis of PPMS and at least 3 years of Expanded Disability Status Scale (EDSS) evaluations and 3 years of follow-up.

Main outcomes and measures The risk of reaching an EDSS score of 7.0 was assessed through multivariable Cox regression models.

Exposures Patients who received DMT before the outcome were considered treated. DMT was assessed as a time-dependent variable and by class of DMT (moderately and highly effective).

Results From a total of 3298 patients with PPMS, 2633 were excluded because they did not meet the entry criteria for the phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy and safety of ocrelizumab in adults with PPMS (ORATORIO) trial. Among the remaining 665 patients (mean [SD] age, 43.0 [10.7] years; 366 female patients [55.0%]), 409 were further selected for propensity score matching (288 treated and 121 untreated patients). In the matched cohort, during the study follow-up, 37% of patients (152 of 409) reached an EDSS score of 7.0 after a mean (SD) follow-up of 10.6 (5.6) years. A higher EDSS score at baseline (adjusted hazard ratio [aHR], 1.32; 95% CI, 1.13-1.55; P < .001), superimposed relapses (aHR, 2.37; 95% CI, 1.24-4.54; P = .009), and DMT exposure (aHR, 1.75; 95% CI, 1.04-2.94; P = .03) were associated with a higher risk of an EDSS score of 7.0, whereas the interaction term between DMT and superimposed relapses was associated with a reduced risk of EDSS score of 7.0 (aHR, 0.33; 95% CI, 0.16-0.71; P = .004). Similar findings were obtained when treatment according to DMT class was considered and when DMT was included as a time-dependent covariate. These results were confirmed in the subgroup of patients with available magnetic resonance imaging data.

Conclusions and relevance Results of this comparative effectiveness research study suggest that inflammation also occurs in patients with PPMS, may contribute to long-term disability, and may be associated with a reduced risk of becoming wheelchair dependent by current licensed DMTs.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Assessing Efficacy and Safety of treatments in progressive Multiple Sclerosis

PRINCIPAL INVESTIGATOR

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Do patients' and referral centers' characteristics influence multiple sclerosis phenotypes? Results from the Italian Multiple Sclerosis and Related Disorders Register

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ABSTRACT

Background Multiple sclerosis (MS) is characterized by phenotypical heterogeneity, partly resulting from demographic and environmental risk factors. Socio-economic factors and the characteristics of local MS facilities might also play a part.

Methods This study included patients with a confirmed MS diagnosis enrolled in the Italian MS and Related Disorders Register in 2000–2021. Patients at first visit were classified as having a clinically isolated syndrome (CIS), relapsing–remitting (RR), primary progressive (PP), progressive-relapsing (PR), or secondary progressive MS (SP). Demographic and clinical characteristics were analyzed, with centers' characteristics, geographic macro-areas, and Deprivation Index. We computed the odds ratios (OR) for CIS, PP/PR, and SP phenotypes, compared to the RR, using multivariate, multinomial, mixed effects logistic regression models.

Results In all 35,243 patients from 106 centers were included. The OR of presenting more advanced MS phenotypes than the RR phenotype at first visit significantly diminished in relation to calendar period. Females were at a significantly lower risk of a PP/PR or SP phenotype. Older age was associated with CIS, PP/PR, and SP. The risk of a longer interval between disease onset and first visit was lower for the CIS phenotype, but higher for PP/PR and SP. The probability of SP at first visit was greater in the South of Italy.

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

DESCRIPTIVE EPIDEMIOLOGY

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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

PRINCIPAL INVESTIGATOR

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Progression is independent of relapse activity in early multiple sclerosis: a real-life cohort study

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ABSTRACT

Disability accrual in multiple sclerosis may occur as relapse-associated worsening or progression independent of relapse activity. The role of progression independent of relapse activity in early multiple sclerosis is yet to be established. The objective of this multicentre, observational, retrospective cohort study was to investigate the contribution of relapse-associated worsening and progression independent of relapse activity 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 (n = 5169). Data were extracted from the Italian Multiple Sclerosis Register. 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. Over a follow-up period of 11.5 ± 5.5 years, progression independent of relapse activity occurred in 1427 (27.6%) and relapse-associated worsening in 922 (17.8%) patients. Progression independent of relapse activity was associated with older age at baseline [hazard ratio (HR) = 1.19; 95% confidence interval (CI) 1.13-1.25, P < 0.001], having a relapsing-remitting course at baseline (HR = 1.44; 95% CI 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; 95% CI 0.88-0.96, P < 0.001) and lower number of relapses before the event (HR = 0.76; 95% CI 0.73-0.80, P < 0.001). Relapse-associated worsening was associated with younger age at baseline (HR = 0.87; 95% CI 0.81-0.93, P < 0.001), having a relapsing-remitting course at baseline (HR = 1.55; 95% CI 1.35-1.79, P < 0.001), lower Expanded Disability Status Scale at baseline (HR = 0.94; 95% CI 0.89-0.99, P = 0.017) and a higher number of relapses before the event (HR = 1.04; 95% CI 1.01-1.07, P < 0.001). Longer exposure to disease-modifying drugs was associated with a lower risk of both progression independent of relapse activity and relapse-associated worsening (P < 0.001). This study provides evidence that in an early relapsing-onset multiple sclerosis cohort, progression independent of relapse activity 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.

MS AND RD COURSES

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Silent progression in an Italian CIS and Relapsing-Remitting multiple sclerosis cohort

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Comparing Natural History of Early and Late Onset Pediatric Multiple Sclerosis

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De Meo E, Filippi M, Trojano M, Comi G, Patti F, Brescia Morra V, Salemi G, Onofrj M, Lus G, Cocco E, Fonderico M, Torri Clerici V, Maniscalco GT, Valentino P, Bertolotto A, Lugaresi A, Bergamaschi R, Rovaris M, Sola P, Tedeschi G, Pesci I, Aguglia U, Cavalla P, Maimone D, Granella F, Vianello M, Simone M, Portaccio E, Amato MP. *Comparing Natural History of Early and Late Onset Pediatric Multiple Sclerosis.* **Ann Neurol. 2022** Apr; 91(4):483-495. doi: 10.1002/ana.26322.

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ABSTRACT

Objective This study was undertaken to describe and compare disease course and prognosis of early (ie, disease onset before age 11 years) and late (ie, disease onset after age 11 years) onset pediatric multiple sclerosis.

Methods Prospectively collected clinical information from Italian Multiple Sclerosis Register of 1993 pediatric multiple sclerosis patients, of whom 172 had early onset, was analyzed. Cox models adjusted for sex, baseline Expanded Disability Status Scale score, and disease-modifying treatments and stratified for diagnostic criteria adopted (Poser vs McDonald) were used to assess the risk of reaching irreversible Expanded Disability Status Scale scores of 3, 4, and 6, and conversion to secondary progressive phenotype in early versus late onset pediatric patients. Prognostic factors were also evaluated.

Results A greater proportion of males, isolated brainstem involvement, and longer time interval between first and second clinical episode were observed in early versus late onset pediatric patients. Compared to late onset, early onset pediatric patients took longer from disease onset to convert to secondary progressive phenotype and to reach all disability milestones. Recovery from first demyelinating event, time to first relapse, annualized relapse rate during the first 3 years of disease, and disease-modifying treatment exposure were independent predictors for long-term disability in early onset pediatric patients. In late onset pediatric patients, isolated optic neuritis, multifocal symptoms, and progressive course at disease onset were additional predictors for long-term disability.

Interpretation These findings point toward the existence of a different natural history in early versus late onset pediatric multiple sclerosis patients.

THERAPY - PROGNOSTIC FACTORS AND PREDICTIVE MODELS OF TREATMENT RESPONSE

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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

PRINCIPAL INVESTIGATOR

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Real world comparison of teriflunomide and dimethyl fumarate in naïve relapsing multiple sclerosis patients: Evidence from the Italian MS register

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Zanghì A, Avolio C, Amato MP, Filippi M, Trojano M, Patti F, 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** Feb; 58:103489. doi: 10.1016/j.msard.2022.103489.

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ABSTRACT

Background Teriflunomide (TERI) and dimethyl fumarate (DMF) are licensed as first-line disease-modifying treatments (DMTs) for relapsing remitting Multiple Sclerosis (RRMS) and are largely replacing injectable DMTs.

Methods All RRMS patients starting TERI or DMF between January 1, 2013, and December 31, 2017, were included in the analysis. Time to first relapse, time to confirmed disability progression (CDP), and time to DMT discontinuation have been investigated. Propensity score with inverse probability treatment weighting (IPTW-PS) was used to adjust comparisons for baseline confounders. The aim of the study was to compare the effectiveness, and rate of discontinuation of TERI and DMF as first therapeutic choice in the Italian MS register.

Results A total of 683 patients were considered for the analyses, 185 on TERI and 498 on DMF. Patients on TERI had higher number of relapses (2.3 ± 1.4 vs 1.9 ± 1.1, p=.033) and higher baseline disability level assessed by Expanded Disability Status Scale (EDSS) (2.0, interquartile range-IQR 1.0–3.0 vs 1.5, IQR 1.0–2.0, p=.013). IPTW adjusted Cox models did not reveal any difference between the investigated DMTs for the investigated outcomes.

Conclusions TERI and DMF have similar effectiveness and rate of discontinuation when employed as first therapeutic choice in RRMS patients.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Comparative effectiveness of initial Treatment Choices for Multiple Sclerosis: a multicentre study

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Risk of Getting COVID-19 in People With Multiple Sclerosis: A Case-Control Study

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ABSTRACT

Background and Objectives Several studies have assessed risk factors associated with the severity of COVID-19 outcomes in people with multiple sclerosis (PwMS). The potential role of disease-modifying therapies (DMTs) and demographic and clinical factors on the risk of acquiring SARS-CoV-2 infection has not been evaluated so far. The objective of this study was to assess risk factors of contracting SARS-CoV-2 infection in PwMS by using data collected in the Italian MS Register (IMSR).

Methods A case-control (1:2) studwy was set up. Cases included PwMS with a confirmed diagnosis of COVID-19, and controls included 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 were included in this study. COVID-19 risk was estimated by multivariable logistic regression models including demographic and clinical covariates. The impact of DMTs was assessed in 3 independent logistic regression models including one of the following covariates: last administered DMT, previous DMT sequences, or the place where the last treatment was administered.

Results A total of 779 PwMS with confirmed COVID-19 (cases) were matched to 1,558 PwMS without COVID-19 (controls). In all 3 models, comorbidities, female sex, and a younger age were significantly associated ($p < 0.02$) with 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 significant higher risk than those taking self-administered DMTs at home.

Discussion This case-control study embedded in the IMSR showed that PwMS at higher COVID-19 risk are younger, more frequently female individuals, and with comorbidities. Long-lasting escalation approach and last therapies that expose patients to the hospital environment seem to significantly increase the risk of SARS-CoV2 infection in PwMS.

Classification of Evidence This study provides Class III evidence that among patients with MS, younger age, being female individuals, having more comorbidities, receiving natalizumab, undergoing an escalating treatment strategy, or receiving treatment at a hospital were 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, whereas not being on treatment or receiving an interferon beta agent was protective.

ANALYTICAL EPIDEMIOLOGY

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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

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First-line therapies in late-onset multiple sclerosis: An Italian registry study

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ABSTRACT

Background and purpose The diagnosis of late-onset (age ≥50 years old) relapsing remitting multiple sclerosis (LORRMS) has been increasingly described in clinical practice, whereas data focusing on the specific therapeutic management of LORRMS are scarce. Our objective was to compare the effectiveness of injectable and oral first-line disease-modifying therapies (DMTs) in a cohort of LORRMS patients with time to first relapse, time to confirmed disability progression (CDP), and time to discontinuation.

Methods This is a multicenter, observational, retrospectively acquired cohort study on LORRMS-naïve patients from the Italian MS Register who started either injectable or oral first-line DMTs between January 1, 2013 and December 31, 2017. LORRMS patients were divided into two groups, namely the injectable group (IG) and oral group (OG). Cox models adjusted with inverse probability-weighted propensity score were built for the investigated outcomes.

Results Of a cohort of 3989 patients, 302 were enrolled (203 in the IG and 99 in the OG). The two cohorts did not differ in baseline characteristics. Time to first relapse did not show any difference between the two groups (hazard ratio [HR]: 1.10; 95% confidence interval [CI]: 0.50-2.46, p = 0.797). Furthermore, no differences were found between the two groups with respect to the risk of CDP (HR: 1.04; 95% CI: 0.35-3.06, p = 0.939), nor for the risk of DMT discontinuation (HR: 0.90; 95% CI: 0.17-2.08, p = 0.425).

Conclusions Real-world data from the Italian MS Register suggested that both injectables and oral first-line DMTs similarly controlled the investigated outcomes in LORRMS.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Comparative effectiveness of initial Treatment Choices for Multiple Sclerosis: a multicentre study

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Risk of multiple sclerosis relapses when switching from fingolimod to cell depleting agents: the role of washout duration

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ABSTRACT

Background Fingolimod (FTY) induces sequestration of lymphocytes in secondary lymphoid organs and the average lymphocyte recovery following discontinuation takes 1–2 months. It has been hypothesized that the therapeutic effects of subsequent cell-depleting agents may be compromised if initiated before lymphocyte recovery has occurred.

Objective To assess the risk of relapses following FTY discontinuation and the initiation of a B/T cell-depleting agent in relation to washout duration using data from the Italian MS Register.

Methods The risk of relapses was assessed in relation to different washout durations (< 6, 6–11, 12–17 and > / = 18 weeks) in patients starting alemtuzumab, rituximab, ocrelizumab or cladribine following FTY discontinuation.

Results We included 329 patients in the analysis (226F, 103 M; mean age 41 ± 10 years). During the cell-depleting treatment, the incidence rate ratio for a relapse was significantly greater in patients with a washout period of 12–17 and > / = 18 weeks compared to the reference period (< 6 weeks). The risk of a relapse was significantly influenced by the occurrence of relapses during FTY treatment and by washout length, with hazard ratios markedly increasing with the washout duration.

Conclusion The risk of relapses increases with the washout duration when switching from FTY to lymphocyte-depleting agents.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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

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PML risk is the main factor driving the choice of discontinuing natalizumab in a large multiple sclerosis population: results from an Italian multicenter retrospective study

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ABSTRACT

Background Natalizumab (NTZ) is an effective treatment for relapsing–remitting multiple sclerosis (RRMS). However, patients and physicians may consider discontinuing NTZ therapy due to safety or efficacy issues. The aim of our study was to evaluate the NTZ discontinuation rate and reasons of discontinuation in a large Italian population of RRMS patients.

Materials and methods The data were extracted from the Italian MS registry in May 2018 and were collected from 51,845 patients in 69 Italian multiple sclerosis centers. MS patients with at least one NTZ infusion in the period between June 1st 2012 to May 15th 2018 were included. Discontinuation rates at each time point were calculated. Reasons for NTZ discontinuation were classified as "lack of efficacy", "progressive multifocal leukoencephalopathy (PML) risk" or "other".

Results Out of 51,845, 5151 patients, 3019 (58.6%) females, with a mean age of 43.6±10.1 years (median 40), were analyzed. Out of 2037 (39.5%) who discontinued NTZ, a significantly higher percentage suspended NTZ because of PML risk compared to lack of efficacy [1682 (32.7% of 5151) vs 221 (4.3%), p<0.001]; other reasons were identified for 99 (1.9%) patients. Patients discontinuing treatment were older, had longer disease duration and worse EDSS at the time of NTZ initiation and at last follow-up on NTZ treatment. The JCV index and EDSS at baseline were predictors for stopping therapy (HR 2.94, 95% CI 1.22–4.75; p=0.02; HR 1.36, 95% CI 1.18–5.41; p=0.04).

Conclusion Roughly 60% of MS patients stayed on NTZ treatment during the observation period. For those patients in whom NTZ discontinuation was required, it was mainly due to PML concerns.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Comparative effectiveness of different Natalizumab dosing schedules in real world life: a retrospective Italian multicentre study

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Risk of Persistent Disability in Patients With Pediatric-Onset Multiple Sclerosis

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ABSTRACT

Importance 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 whether this improvement also involves patients with pediatric-onset MS (POMS), whose early management is more challenging.

Objective To evaluate changes in the prognosis of POMS over time in association with changes in therapeutic and managing standards.

Design, setting, and participants Retrospective, multicenter, observational study. Data were extracted and collected in May 2019 from the Italian MS Registry, a digital database including more than 59 000 patients. Inclusion criteria were MS onset before age 18 years, diagnosis before January 2014, and disease duration of at least 3 years. Exclusion criteria were primary progressive MS, Expanded Disability Status Scale (EDSS) score of at least 8 one year after onset, unavailability of diagnosis date, and less than 2 EDSS score evaluations. Eligible patients were 4704 patients with POMS. According to these criteria, we enrolled 3198 patients, excluding 1506.

Exposures We compared time to reach disability milestones by epoch of MS diagnosis (<1993, 1993-1999, 2000-2006, and 2007-2013), adjusting for possible confounders linked to EDSS evaluations and clinical disease activity. We then analyzed the difference among the 4 diagnosis epochs regarding demographic characteristics, clinical disease activity at onset, and DMTs management.

Main outcomes and measures Disability milestones were EDSS score 4.0 and 6.0, confirmed in the following clinical evaluation and in the last available visit.

Results We enrolled 3198 patients with POMS (mean age at onset, 15.2 years; 69% female; median time to diagnosis, 3.2 years; annualized relapse rate in first 1 and 3 years, 1.3 and 0.6, respectively), with a mean (SD) follow-up of 21.8 (11.7) years. Median survival times to reach EDSS score of 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 score of 4.0 (hazard ratio [HR], 0.70; 95% CI, 0.58-0.83 in 1993-1999; HR, 0.48; 95% CI, 0.38-0.60 in 2000-2006; and HR, 0.44; 95% CI, 0.32-0.59 in 2007-2013) and 6.0 (HR, 0.72; 95% CI, 0.57-0.90; HR, 0.44; 95% CI, 0.33-0.60; and HR, 0.30; 0.20-0.46). In later diagnosis epochs, a greater number of patients with POMS 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.

Conclusions and relevance In POMS, the risk of persistent disability has been reduced by 50% to 70% in recent diagnosis epochs, probably owing to improvement in therapeutic and managing standards.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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

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Long-term disability trajectories in relapsing multiple sclerosis patients treated with early intensive or escalation treatment strategies

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ABSTRACT

Background and aims No consensus exists on how aggressively to treat relapsing-remitting multiple sclerosis (RRMS) nor on the timing of the treatment. The objective of this study was to evaluate disability trajectories in RRMS patients treated with an early intensive treatment (EIT) or with a moderate-efficacy treatment followed by escalation to higher-efficacy disease modifying therapy (ESC).

Methods RRMS patients with ≥5-year follow-up and ≥3 visits after disease modifying therapy (DMT) start were selected from the Italian MS Registry. EIT group included patients who received as first DMT fingolimod, natalizumab, mitoxantrone, alemtuzumab, ocrelizumab, cladribine. ESC group patients received the high efficacy DMT after ≥1 year of glatiramer acetate, interferons, azathioprine, teriflunomide or dimethylfumarate 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 Expanded Disability Status Scale (EDSS) changes compared with baseline values (delta-EDSS) in EIT and ESC groups.

Results The study cohort included 2702 RRMS patients. The PS matching procedure produced 363 pairs, followed for a median (interquartile range) of 8.5 (6.5-11.7) years. Mean annual delta-EDSS values were all significantly ($p < 0.02$) higher in the ESC group compared with the EIT group. In particular, the mean delta-EDSS differences between the two groups tended to increase from 0.1 (0.01-0.19, $p = 0.03$) at 1 year to 0.30 (0.07-0.53, $p = 0.009$) at 5 years and to 0.67 (0.31-1.03, $p = 0.0003$) at 10 years.

Conclusion Our results indicate that EIT strategy is more effective than ESC strategy in controlling disability progression over time.

THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Early-aggressive treatment algorithm versus classical escalation therapy in relapsing Multiple Sclerosis

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Early treatment delays long-term disability accrual in RRMS: Results from the BMSD network

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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.

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ABSTRACT

Background The optimal timing of treatment starts for achieving the best control on the long-term disability accumulation in multiple sclerosis (MS) is still to be defined.

Objective The aim of this study was to estimate the optimal time to start disease-modifying therapies (DMTs) to prevent the long-term disability accumulation in MS, using a pooled dataset from the Big Multiple Sclerosis Data (BMSD) network.

Methods Multivariable Cox regression models adjusted for the time to first treatment start from disease onset (in quintiles) were used. To mitigate the impact of potential biases, a set of pairwise propensity score (PS)-matched analyses were performed. The first quintile, including patients treated within 1.2 years from onset, was used as reference.

Results A cohort of 11,871 patients (median follow-up after treatment start: 13.2 years) was analyzed. A 3- and 12-month confirmed disability worsening event and irreversible Expanded Disability Status Scale (EDSS) 4.0 and 6.0 scores were reached by 7062 (59.5%), 4138 (34.9%), 3209 (31.1%), and 1909 (16.5%) patients, respectively. The risk of reaching all the disability outcomes was significantly lower ($p < 0.0004$) for the first quintile patients' group.

Conclusion Real-world data from the BMSD demonstrate that DMTs should be commenced within 1.2 years from the disease onset to reduce the risk of disability accumulation over the long term.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Big Multiple Sclerosis Data (BMSD) Network

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Injectable Versus Oral First-Line Disease-Modifying Therapies: Results from the Italian MS Register

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D'Amico E, Zanghì A, Romeo M, Cocco E, Maniscalco GT, Brescia Morra V, Paolicelli D, De Luca G, Galgani S, Amato MP, Salemi G, Inglese M, Confalonieri PA, Lus G, Avolio C, Gallo A, Vianello M, Onofrj M, Filippi M, Trojano M, Patti F. *Injectable Versus Oral First-Line Disease-Modifying Therapies: Results from* **the Italian MS Register. Neurotherapeutics. 2021** Apr;18(2):905-919. doi: 10.1007/s13311-020-01001-6.

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ABSTRACT

The current study aims to compare injectable and oral first-line disease-modifying therapies (DMTs) for time to first relapse, time to confirmed disability progression (CDP), and time to discontinuation using a cohort of relapsing remitting multiple sclerosis (RRMS) patients, with data extracted from the Italian MS Register. 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. Enrolled patients were divided into two groups, namely the injectable group (IG) and the oral group (OG). Of a cohort of 11,416 patients, 4602 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. 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.

THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Comparative effectiveness of initial Treatment Choices for Multiple Sclerosis: a multicentre study

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Treatment Switching and Discontinuation Over 20 Years in the Big Multiple Sclerosis Data Network

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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**;12:647811. doi: 10.3389/fneur.2021.647811.

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ABSTRACT

Background Although over a dozen disease modifying treatments (DMTs) are available for relapsing forms of multiple sclerosis (MS), treatment interruption, switching and discontinuation are common challenges. The objective of this study was to describe treatment interruption and discontinuation in the Big MS data network.

Methods We merged information on 269,822 treatment episodes in 110,326 patients from 1997 to 2016 from five clinical registries in this cohort study. 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.

Results The incidence of DMT stopping cross the full observation period was lowest in FTY (19.7 per 100 person-years (PY) of treatment; 95% CI 19.2-20.1), followed by NAT (22.6/100 PY; 95% CI 22.2-23.0), IFNβ (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. Reasons for stopping a drug were stable during the observation period with lack of efficacy being the most common reason followed by lack of tolerance and side effects. The proportion of patients continuing on most DMTs were similarly stable until 2014 and 2015 when drop from 83 to 75% was noted.

Conclusions DMT stopping reasons and rates were mostly stable over time with a slight increase in recent years, with the availability of more DMTs. The overall 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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Big Multiple Sclerosis Data (BMSD) Network

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Transition to secondary progression in relapsing-onset multiple sclerosis: Definitions and risk factors

REFERENCE
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.

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ABSTRACT

Background No uniform criteria for a sensitive identification of the transition from relapsing-remitting multiple sclerosis (MS) to secondary-progressive multiple sclerosis (SPMS) are available.

Objective To compare risk factors of SPMS using two definitions: one based on the neurologist judgment (ND) and an objective data-driven algorithm (DDA).

Methods Relapsing-onset MS patients (n = 19,318) were extracted from the Italian MS Registry. Risk factors for SPMS and for reaching irreversible Expanded Disability Status Scale (EDSS) 6.0, after SP transition, were estimated using multivariable Cox regression models.

Results SPMS identified by the DDA (n = 2343, 12.1%) were older, more disabled and with a faster progression to severe disability ($p < 0.0001$), than those identified by the ND (n = 3868, 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 disease-modifying therapy (DMT) exposure. DMT exposure during SP did not impact the risk of reaching irreversible EDSS 6.0.

Conclusion A DDA definition of SPMS identifies more aggressive progressive patients. DMT exposure reduces the risk of SPMS conversion, but it does not prevent the disability accumulation after the SP transition.

THERAPY - PROGNOSTIC FACTORS AND PREDICTIVE MODELS OF TREATMENT RESPONSE

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

INSPIRA - Italian analysis of the National multiple sclerosis registry Studying the concept of Progression Independent from Relapse Activity

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Detection of disability worsening in relapsing-remitting multiple sclerosis patients: a real-world roving Expanded Disability Status Scale reference analysis from the Italian Multiple Sclerosis Register

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Lepore V, Bosetti C, Santucci C, Iaffaldano P, Trojano M, Mosconi P; **Italian Multiple Sclerosis Register Centers Group, the Scientific Committee of Italian SM Register.** *Detection of disability worsening in relapsing-remitting multiple sclerosis patients: a real-world roving Expanded Disability Status Scale reference analysis from the* **Italian Multiple Sclerosis Register. Eur J Neurol. 2021** Feb;28(2):567-578. doi: 10.1111/ene.14589.

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ABSTRACT

Background and purpose In relapsing-remitting multiple sclerosis patients (RRMS) disability progressively accumulates over time. To compare the cumulative probability of 6-month confirmed disability-worsening events using a fixed baseline or a roving Expanded Disability Status Scale (EDSS) reference, in a real-world setting.

Methods A cohort of 7964 RRMS patients followed for 2 or more years, with EDSS scores recorded every 6 months, was selected from the Italian Multiple Sclerosis Register. The overall probability of confirmed disability-worsening events and of confirmed disability-worsening events unrelated to relapse was evaluated using as reference a fixed baseline EDSS score or a roving EDSS score in which the increase had to be separated from the last EDSS assessment by at least 6 or 12 months.

Results Using a fixed baseline EDSS reference, the cumulative probability of 6-year overall confirmed disability-worsening events was 33.2%, and 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).

Conclusions In a real-world setting, roving EDSS reference scores appear to be more sensitive for detecting confirmed disability-worsening events unrelated to relapse in RRMS patients.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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

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Chisari CG, Grimaldi LM, Salemi G, Ragonese P, Iaffaldano P, Bonavita S, Sparaco M, Rovaris M, D'Arma A, Lugaresi A, Ferrò MT, Grossi P, Di Sapio A, Cocco E, Granella F, Curti E, Lepore V, Trojano M, Patti F; **Italian MS Register** Study Group. *Clinical effectiveness of different natalizumab interval dosing schedules in a large Italian population of patients with multiple sclerosis.* **J Neurol Neurosurg Psychiatry. 2020** Dec;91(12):1297-1303. doi: 10.1136/jnnp-2020-323472.

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ABSTRACT

Introduction Natalizumab (NTZ) is one of the most effective treatment options for multiple sclerosis (MS) treatment. Our study aimed to evaluate the effectiveness of NTZ when administered according to the extended dosing strategy compared with standard 4-weekly administration in a large Italian MS population.

Materials and methods This retrospective multicentre study included patients with relapsing-remitting MS (RR-MS) who received NTZ administrations between the 1 June 2012 and the 15 May 2018 and were followed by the 'Italian MS Register'. All patients with MS were stratified into two groups based on NTZ administration schedule: standard interval dosing (SID) patients who received infusions on average from 28 to 32 days (median 30) and extended interval dosing (EID) including patients who have been infused with interval between 33 and 49 days (median 43). Clinical data were assessed at baseline (before starting NTZ), after 12 (T1) and 24 months (T2) of treatment.

Results Out of 5231 patients with RR-MS screened, 2092 (mean age 43.2±12.0, 60.6% women) were enrolled. A total of 1254 (59.9%) received NTZ according to SID, and 838 (40.1%) according to EID. At 12 and 24 months, no differences in terms of annualised relapse rate and disability status were found between the two groups. Progression index and confirmed disability worsening were similar between the two groups.

Discussion 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.

THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Comparative effectiveness of different Natalizumab dosing schedules in real world life: a retrospective Italian multicentre study

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Disease-modifying drugs can reduce disability progression in relapsing multiple sclerosis

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ABSTRACT

An ever-expanding number of disease-modifying drugs for multiple sclerosis have become available in recent years, after demonstrating efficacy in clinical trials. In the real-world setting, however, disease-modifying drugs are prescribed in patient populations that differ from those included in pivotal studies, where extreme age patients are usually excluded or under-represented. In this multicentre, observational, retrospective Italian cohort study, we evaluated treatment exposure in three cohorts of patients with relapsing-remitting multiple sclerosis defined by age at onset: paediatric-onset (≤18 years), adult-onset (18-49 years) and late-onset multiple sclerosis (≥50 years). We included patients with a relapsing-remitting phenotype, ≥5 years follow-up, ≥3 Expanded Disability Status Scale (EDSS) evaluations and a first neurological evaluation 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 EDSS 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 paediatric-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 paediatric-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 (0.9-4.1), P = 0.07]. These results were confirmed for a sustained EDSS score of 4.0. We also found that relapses were a risk factor for 12-month confirmed disability worsening in all three cohorts, and female sex exerted a protective role in the late-onset cohort. 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.

MS AND RD COURSES

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

E-MUSIC: Early MUltiple Sclerosis Italian Cohort

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Long-term effectiveness in patients previously treated with cladribine tablets: a real-world analysis of the Italian multiple sclerosis registry (CLARINET-MS)

REFERENCE
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

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ABSTRACT

Background 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.

Methods Real-world data (RWD) from Italian MS patients who participated in cladribine tablets randomised clinical trials (RCTs; CLARITY, CLARITY Extension, ONWARD or ORACLE-MS) 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.

Conclusion 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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

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

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Retrospectively acquired cohort study to evaluate the long-term impact of two different treatment strategies on disability outcomes in patients with relapsing multiple sclerosis (RE.LO.DI.MS): data from the Italian MS Register

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ABSTRACT

Background 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.

Objective To evaluate different therapeutic strategies and their long-term outcomes, measured as relapses and confirmed disability progression (CDP), in MS 'real-world' settings.

Methods Multicentre, observational, retrospectively acquired cohort study evaluating 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].

Conclusion 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.

THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA:

Retrospective study to evaluate the long-term impact of different treatment strategies on disability outcomes in patients with relapsing multiple sclerosis. Italian IMedWeb MS Registry. RE.LO.DI.MS Study

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The Italian Multiple Sclerosis Register

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Trojano M, Bergamaschi R, Amato MP, Comi G, Ghezzi A, Lepore V, Marrosu MG, Mosconi P, Patti F, Ponzio M, Zaratin P, Battaglia MA; **Italian Multiple Sclerosis Register Centers Group. The Italian multiple sclerosis register. Neurol Sci. 2019** Jan;40(1):155-165. doi: 10.1007/s10072-018-3610-0.

Erratum in Correction to: The Italian multiple sclerosis register.

Trojano M, Bergamaschi R, Amato MP, Comi G, Ghezzi A, Lepore V, Marrosu MG, Mosconi P, Patti F, Ponzio M, Zaratin P, Battaglia MA; **Italian Multiple Sclerosis Register Centers Group. The Italian multiple sclerosis register.** Neurol Sci. 2019 Jan;40(1):155-165. doi: 10.1007/s10072-018-3610-0. Epub 2018 Nov 13. Erratum in: **Neurol Sci. 2019** Apr;40(4):907.

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ABSTRACT

The past decade has seen extraordinary increase in worldwide availability of and access to several large multiple sclerosis (MS) databases and registries. MS registries represent powerful tools to provide meaningful information on the burden, natural history, and long-term safety and effectiveness of treatments. Moreover, patients, physicians, industry, and policy makers have an active interest in real-world observational studies based on register data, as they have the potential to answer the questions that are most relevant to daily treatment decision-making. In 2014, the Italian MS Foundation, in collaboration with the Italian MS clinical centers, promoted and funded the creation of the Italian MS Register, a project in continuity with the existing Italian MS Database Network set up from 2001. Main objective of the Italian MS Register is to create an organized multicenter structure to collect data of all MS patients for better defining the disease epidemiology, improving quality of care, and promoting research projects in high-priority areas. The aim of this article is to present the current framework and network of the Italian MS register, including the methodology used to improve the quality of data collection and to facilitate the exchange of data and the collaboration among national and international groups.

Prognostic indicators in pediatric clinically isolated syndrome

REFERENCE

Iaffaldano P, Simone M, Lucisano G, Ghezzi A, Coniglio G, Brescia Morra V, Salemi G, Patti F, Lugaresi A, Izquierdo G, Bergamaschi R, Cabrera-Gomez JA, Pozzilli C, Millefiorini E, Alroughani R, Boz C, Pucci E, Zimatore GB, Sola P, Lus G, Maimone D, Avolio C, Cocco E, Sajedi SA, Costantino G, Duquette P, Shaygannejad V, Petersen T, Fernández Bolaños R, Paolicelli D, Tortorella C, Spelman T, Margari L, Amato MP, Comi G, Butzkueven H, Trojano M; **Italian iMedWeb Registry** and the MSBase Registry. *Prognostic indicators in pediatric clinically isolated syndrome.* **Ann Neurol. 2017** May;81(5):729-739. doi: 10.1002/ana.24938.

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Italian iMedWeb Registry and the MSBase Registry

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ABSTRACT

Objective To assess prognostic factors for a second clinical attack and a first disability-worsening event in pediatric clinically isolated syndrome (pCIS) suggestive of multiple sclerosis (MS) patients.

Methods A cohort of 770 pCIS patients was followed up for at least 10 years. Cox proportional hazard models and Recursive Partitioning and Amalgamation (RECPAM) tree-regression were used to analyze data.

Results In pCIS, female sex and a multifocal onset were risk factors for a second clinical attack (hazard ratio [HR], 95% confidence interval [CI] = 1.28, 1.06-1.55; 1.42, 1.10-1.84, respectively), whereas disease-modifying drug (DMD) exposure reduced this risk (HR, 95% CI = 0.75, 0.60-0.95). After pediatric onset MS (POMS) diagnosis, age at onset younger than 15 years and DMD exposure decreased the risk of a first Expanded Disability Status Scale (EDSS)-worsening event (HR, 95% CI = 0.59, 0.42-0.83; 0.75, 0.71-0.80, respectively), whereas the occurrence of relapse increased this risk (HR, 95% CI = 5.08, 3.46-7.46). An exploratory RECPAM analysis highlighted a significantly higher incidence of a first EDSS-worsening event in patients with multifocal or isolated spinal cord or optic neuritis involvement at onset in comparison to those with an isolated supratentorial or brainstem syndrome. A Cox regression model including RECPAM classes confirmed DMD exposure as the most protective factor against EDSS-worsening events and relapses as the most important risk factor for attaining EDSS worsening.

Interpretation This work represents a step forward in identifying predictors of unfavorable course in pCIS and POMS and supports a protective effect of early DMD treatment in preventing MS development and disability accumulation in this population.

Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis

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Iaffaldano P, Lucisano G, Pozzilli C, Brescia Morra V, Ghezzi A, Millefiorini E, Patti F, Lugaresi A, Zimatore GB, Marrosu MG, Amato MP, Bertolotto A, Bergamaschi R, Granella F, Coniglio G, Tedeschi G, Sola P, Lus G, Ferrò MT, Iuliano G, Corea F, Protti A, Cavalla P, Guareschi A, Rodegher M, Paolicelli D, Tortorella C, Lepore V, Prosperini L, Saccà F, Baroncini D, Comi G, Trojano M; **Italian iMed-Web database**. *Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis*. **Brain. 2015** Nov;138(Pt 11):3275-86. doi: 10.1093/brain/awv260.

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Italian iMed-Web database

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ABSTRACT

The comparative effectiveness of fingolimod versus interferon beta/glatiramer acetate was assessed in a multicentre, observational, prospectively acquired cohort study including 613 patients with relapsing multiple sclerosis discontinuing natalizumab in the Italian iMedWeb registry. First, after natalizumab suspension, the relapse risk during the untreated wash-out period and during the course of switch therapies was estimated through Poisson regression analyses in separated models. During the wash-out period an increased risk of relapses was found in patients with a higher number of relapses before natalizumab treatment (incidence rate ratio = 1.31, P = 0.0014) and in patients discontinuing natalizumab due to lack of efficacy (incidence rate ratio = 2.33, P = 0.0288), patient's choice (incidence rate ratio = 2.18, P = 0.0064) and adverse events (incidence rate ratio = 2.09, P = 0.0084). The strongest independent factors influencing the relapse risk after the start of switch therapies were a wash-out duration longer than 3 months (incidence rate ratio = 1.78, P < 0.0001), the number of relapses experienced during and before natalizumab treatment (incidence rate ratio = 1.61, P < 0.0001; incidence rate ratio = 1.13, P = 0.0118, respectively) and the presence of comorbidities (incidence rate ratio = 1.4, P = 0.0097). Switching to fingolimod was associated with a 64% reduction of the adjusted-risk for relapse in comparison with switching to interferon beta/glatiramer acetate (incidence rate ratio = 0.36, P < 0.0001). Secondly, patients who switched to fingolimod or to interferon beta/glatiramer acetate were propensity score-matched on a 1-to-1 basis at the switching date. In the propensity score-matched sample a Poisson model showed a significant lower incidence of relapses in patients treated with fingolimod in comparison with those treated with interferon beta/glatiramer acetate (incidence rate ratio = 0.52, P = 0.0003) during a 12-month follow-up. The cumulative probability of a first relapse after the treatment switch was significantly lower in patients receiving fingolimod than in those receiving interferon beta/glatiramer acetate (P = 0.028). The robustness of this result was also confirmed by sensitivity analyses in subgroups with different wash-out durations (less or more than 3 months). Time to 3-month confirmed disability progression was not significantly different between the two groups (Hazard ratio = 0.58; P = 0.1931). Our results indicate a superiority of fingolimod in comparison to interferon beta/glatiramer acetate in controlling disease reactivation after natalizumab discontinuation in the real life setting.

Real-life impact of early interferonβ therapy in relapsing multiple sclerosis

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Trojano M, Pellegrini F, Paolicelli D, Fuiani A, Zimatore GB, Tortorella C, Simone IL, Patti F, Ghezzi A, Zipoli V, Rossi P, Pozzilli C, Salemi G, Lugaresi A, Bergamaschi R, Millefiorini E, Clerico M, Lus G, Vianello M, Avolio C, Cavalla P, Lepore V, Livrea P, Comi G, Amato MP; **Italian Multiple Sclerosis Database Network (MSDN) Group**. *Real-life impact of early interferon beta therapy in relapsing multiple sclerosis.* **Ann Neurol. 2009** Oct;66(4):513-20. doi: 10.1002/ana.21757.

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ABSTRACT

Objective Recent findings support greater efficacy of early vs. delayed interferon beta (IFNbeta) treatment in patients with a first clinical event suggestive of multiple sclerosis (MS). We aimed to evaluate the effectiveness of early IFNbeta treatment in definite relapsing-remitting MS (RRMS) and to assess the optimal time to initiate IFNbeta treatment with regard to the greatest benefits on disability progression.

Methods A cohort of 2,570 IFNbeta-treated RRMS patients was prospectively followed for up to 7 years in 15 Italian MS Centers. A Cox proportional hazards regression model adjusted for propensity score (PS) quintiles was used to assess differences between groups of patients with early vs. delayed IFNbeta treatment on risk of reaching a 1-point progression in the Expanded Disability Status Scale (EDSS) score, and the EDSS 4.0 and 6.0 milestones. A set of PS-adjusted Cox hazards regression models were calculated according to different times of treatment initiation (within 1 year up to within 5 years from disease onset). A sensitivity analysis was performed to assess the robustness of findings.

Results The lowest hazard ratios (HRs) for the three PS quintiles-adjusted models were obtained by a cutoff of treatment initiation within 1 year from disease onset. Early treatment significantly reduced the risk of reaching a 1-point progression in EDSS score (HR = 0.63; 95% CI = 0.48-0.85; $p < 0.002$), and the EDSS 4.0 milestone (HR = 0.56; 95% CI = 0.36-0.90; $p = 0.015$). Sensitivity analysis showed the bound of significance for unmeasured confounders.

Interpretation Greater benefits on disability progression may be obtained by an early IFNbeta treatment in RRMS.

Post-marketing of disease modifying drugs in multiple sclerosis: an exploratory analysis of gender effect in interferon beta treatment

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Trojano M, Pellegrini F, Paolicelli D, Fuiani A, Zimatore GB, Tortorella C, Simone IL, Patti F, Ghezzi A, Portaccio E, Rossi P, Pozzilli C, Salemi G, Lugaresi A, Bergamaschi R, Millefiorini E, Clerico M, Lus G, Vianello M, Avolio C, Cavalla P, Iaffaldano P, Direnzo V, D'Onghia M, Lepore V, Livrea P, Comi G, Amato MP; **Italian Multiple Sclerosis Database Network Group.** *Post-marketing of disease modifying drugs in multiple sclerosis: an exploratory analysis of gender effect in interferon beta treatment.* **J Neurol Sci. 2009** Nov;286(1-2):109-13. doi: 10.1016/j.jns.2009.06.036.

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ABSTRACT

Background There are a few and conflicting results from randomised controlled trials (RCTs) pertaining to the influence of gender in response to currently used disease modifying drugs in Multiple Sclerosis (MS). Observational studies may be especially valuable for answering effectiveness questions in subgroups not studied in RCTs.

Objective To conduct a post-marketing analysis aimed to evaluate the gender effect on Interferon beta (IFNbeta) treatment response in a cohort of relapsing (RR) MS patients.

Methods A cohort of 2570 IFNbeta-treated RRMS was prospectively followed for up to 7 years in 15 Italian MS Centers. Cox proportional hazards regression models were used to assess gender differences for risk of reaching 1st relapse and risk of progression by 1 point on Expanded Disability Status Scale (EDSS) score. Gender effects were also explored by a propensity score (PS) matching algorithm, and a tree-growing technique.

Results The multivariate Cox Regression analyses showed that male patients had a significant (p=0.0097) lower risk for 1st relapse and a trend (p=0.0897) for a higher risk to reach 1 point EDSS progression than females. The PS matched multivariate Cox Regression confirmed these results. The RECPAM analysis showed that male sex conferred a significant reduction in the risk for 1st relapse (HR=0.86; 95% CI=0.76-0.98; p=0.0226) in the subgroup with a low pre-treatment number of bouts, and a significant increase in the risk for 1 point EDSS progression (HR=1.33; 95% CI: 1.00-1.76; p<0.05) in the subgroup with a delayed treatment, but a still young age at the start of treatment.

Conclusion The results of this exploratory analysis seem to suggest that male patients do not respond to IFNbeta treatment in the same way of females.

The MS Clinical Centers participating in the Register

List of participating MS Clinical Centers divided by Italian Regions

Clinical Center, Principal Investigator, Starting Year of Participation

ABRUZZO

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2024

Divisione di Neurologia
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Centro Sclerosi Multipla
Clinica Neurologica Policlinico SS. Annunziata
Stefano Sensi
2016

Centro Malattie Demielinizzanti
Clinica Neurologica Ospedale San Salvatore
Rocco Totaro
2016

BASILICATA

Centro Sclerosi Multipla
PO Madonna delle Grazie
Maria Gabriella Coniglio
2015

CALABRIA

Ambulatorio SM - Grande Ospedale Metropolitano Bianchi Melacrino Morelli
Umberto Aguglia
2015

Centro SM - Divisione di Neurologia
Ospedale dell'Annunziata
Maria Trotta
2021

Centro Sclerosi Multipla
Policlinico Universitario Campus Germaneto
Paola Valentino
2015

UO di Neurologia - Centro SM
ASP di Cosenza
Roberto Bruno Bossio
2016

CAMPANIA

IRCCS SYNLAB SDN SpA
Carlo Cavaliere
2022

Centro Regionale di Diagnosi e Terapia della Sclerosi Multipla
Giorgia Teresa Maniscalco
2016

Centro Regionale Sclerosi Multipla
Unità Operativa Semplice - AOU Policlinico Federico II
Vincenzo Brescia Morra
2016

Centro Clinico per la Sclerosi Multipla
II Clinica Neurologica - II Università di Napoli
Giacomo Lus
2015

Centro Sclerosi Multipla - UOC Neurologia
AORN San Giuseppe Moscati
Daniele Spitaleri
2015

SC di Neurologia - Dipartimento di Neuroscienze e Riabilitazione - AORN Santobono Pausilipon
Marida Della Corte
2020

Dipartimento di Scienze Mediche e Chirurgiche Avanzate - Università della Luigi Vanvitelli
Antonio Gallo
2015

Divisione Neurologia - Azienda Ospedaliera San Giovanni di Dio e Ruggi

Paolo Barone
2018

UOC Neurologia - UOS Neurofisiologia Dipartimento di Neuroscienze, Scienze Riproduttive ed Odontostomatologiche, Università di Napoli Federico II

Rosa Iodice
2015

Centro SM - UOC di Neurologia Ospedale San Paolo - ASL Napoli 1 Centro

Leonardo Sinisi
2015

UO di Neurologia - Ospedale Maria SS. Addolorata Centro Diagnosi e Terapia Sclerosi Multipla

Vincenzo Busillo
2015

Centro Sclerosi Multipla PO San Giuseppe Moscati

Nicola Capasso
2019

EMILIA ROMAGNA

Ambulatorio Sclerosi Multipla della UO di Neurologia - Ospedale Morgagni Pierantoni - AUSL della Romagna

Silvia Strumia
2015

Centro SM UOC Neurologia - Ospedale di Vaio - AUSL PR

Ilaria Pesci
2015

UOC di Neurologia - Ospedale Ramazzini

Mario Santangelo
2016

Dipartimento di Neuroscienze - Ospedale Civile di Baggiovara - Azienda Ospedaliero-Universitaria

Diana Ferraro
2015

Azienda Unità Sanitaria Locale di Piacenza - Ospedale Guglielmo da Saliceto - UOC Neurologia

Paolo Immovilli
2019

Dipartimento di Neuroscienze - Centro Sclerosi Multipla - UO Neurologia - Ospedale S. Maria delle Croci - AUSL Romagna

Matteo Foschi
2021

Centro Sclerosi Multipla - UOC di Neurologia - Dipartimento di Medicina Generale e Specialistica AOU di Parma

Franco Granella
2015

IRCCS Istituto delle Scienze Neurologiche di Bologna UOSI Riabilitazione Sclerosi Multipla

Alessandra Lugaresi
2015

Centro SM - UOC Neurologia - Arcispedale Santa Maria Nuova - AUSL Reggio Emilia

Sara Montepietra
2015

Centro di Servizio e Ricerca sulla Sclerosi Multipla AOU di Ferrara

Maura Pugliatti
2015

Centro Sclerosi Multipla - UO di Neurologia Ospedale Bufalini

Luca Mancinelli
2016

FRIULI-VENEZIA GIULIA

SOC Neurologia - Day Hospital ASUIUD PO S. Maria Della Misericordia

Daniela Cargnelutti
2015

Divisione Neurologica Ospedale Civile Santa Maria degli Angeli

Laura Locatelli
2022

Centro di Studio e cura Sclerosi Multipla ASUGI Ospedale di Cattinara

Antonio Bosco
2022

Struttura Complessa di Neuropsichiatria Infantile IRCCS Materno Infantile Burlo Garofolo

Marco Carrozzi
2020

Centro SM Clinica Neurologica Udine

Mariarosaria Valente
2023

LAZIO

Centro Clinico Sclerosi Multipla - Ospedale Fatebenefratelli San Pietro

Marco Peresson
2015

Centro Sclerosi Multipla - AO S. Camillo Forlanini,
Carla Tortorella
2015

Centro Sclerosi Multipla - AO San Giovanni Addolorata
Carlo Piantadosi
2015

CENTERS Centro Neurologico Terapie Sperimentali - Sapienza Università di Roma - AO S. Andrea
Marco Salvetti
2015

Centro SM - Policlinico S. Andrea Università Sapienza
Carlo Pozzilli
2015

Centro SM - Fondazione Santa Lucia IRCCS
Maria Grazia Grasso
2015

Centro SM - Ospedale Spaziani
Fabiana Marinelli
2021

Centro per la diagnosi e la cura delle malattie infiammatorie demielinizzanti in età pediatrica - Ospedale Bambino Gesù
Massimiliano Valeriani
2017

UOSD Sclerosi Multipla - Dipartimento Medicina dei Sistemi - Università Tor Vergata
Girolama Alessandra Marfia
2015

UO Sclerosi Multipla - Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore
Massimiliano Mirabella
2015

Dipartimento di Neuroscienze Umane Unità di Neuropsichiatria Infantile Università La Sapienza
Vincenzo Leuzzi
2020

Centro Sclerosi Multipla - Ospedale Belcolle
Nicola Falcone
2019

Centro Regionale Diagnosi e Cura Sclerosi Multipla e Malattie Demielinizzanti - Ospedale Sant'Eugenio
Daniela De Pascalis
2015

Servizio di Neurologia - Ospedale Santa Maria Goretti
Francesco Sica
2021

Centro Sclerosi Multipla - UO di Neurologia Ospedale San Camillo De Lellis
Steno Rinalduzzi
2015

Centro Sclerosi Multipla - AOU del Policlinico Umberto I - Università Sapienza
Antonella Conte
2017

Centro SM - UOC di Neurologia Policlinico Universitario Campus Bio-Medico,
Vincenzo Di Lazzaro
2015

Centro SM - PO San Filippo Neri - ASL Roma 1
Elisabetta Ferraro
2015

LIGURIA

Centro Sclerosi Multipla - Divisione di Neurologia - Ospedale San Paolo
Matteo Pizzorno
2015

Centro SM Pietra Ligure SC Neurologia Ospedale Santa Corona
Tiziana Tassinari
2015

Ambulatorio Sclerosi Multipla Neurologia ASL 4 Chiavarese
Giuseppe Trivelli
2017

Ambulatorio Sclerosi Multipla - EO Ospedali Galliera
Simonetta Venturi
2015

Centro Sclerosi Multipla e Malattie Demielinizzanti - Ospedale Civile S. Andrea - USL 5
Loredana Petrucci
2015

UO Neuropsichiatria Infantile - Dip. Neuroscienze Mediche e Chirurgiche e Riabilitazione - Continuità delle Cure - IRCCS Gaslini
Maria Margherita Mancardi
2020

SC Neurologia - Centro Sclerosi Multipla - Ospedale Padre Antero Micone - ASL3 Genovese
Paola Gazzola
2015

Centro per lo Studio e la Cura della Sclerosi Multipla e Malattie Demielinizzanti - Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili - Clinica Neurologica - Ospedale Policlinico San Martino (DiNOGMI)
Matilde Inglese
2015

UO Neurologia - Dipartimento di Neuroscienze e Organi di Senso - Ospedale Policlinico San Martino
Giuseppe Ribizzi
2015

Ambulatorio Malattie Demielinizzanti - OC Imperia,
Maria Teresa Rilla
2022

Servizio di Riabilitazione AISM
Michela Bruzzone
2017

LOMBARDIA

SC Neurologia Pediatrica - Centro Sclerosi Multipla Pediatrica - Ospedale dei Bambini Buzzi
Stefania Maria Bova
2020

Neurologia ad Indirizzo Neuroimmunologico Centro Sclerosi Multipla - ASST della Valle Olona - Ospedale di Gallarate
Pietro Annovazzi
2015

ASST della Valle Olona - PO di Saronno - Ambulatorio Sclerosi Multipla
Davide Nasuelli
2016

Centro di Riferimento Regionale per la Sclerosi Multipla - Spedali Civili Brescia - PO Montichiari
Nicola De Rossi
2023

Centro di Neuroimmunologia Fondazione IRCCS San Gerardo dei Tintori
Maura Frigo
2015

Fondazione IRCCS Istituto Neurologico Carlo Besta
Valentina Torri Clerici
2015

Centro SM - Fondazione Don Carlo Gnocchi IRCCS
Marco Rovaris
2015

ASST Grande Ospedale Metropolitano Niguarda Centro SM
Alessandra Protti
2015

Azienda Socio Sanitaria Territoriale (ASST) della Franciacorta
Vincenzo Sidoti
2017

Centro SM - Dipartimento di Neuroscienze ASST Ovest Milanese
Serena Leva
2015

Centro Sclerosi Multipla - Ospedale di Desio
Ignazio Santilli
2023

Centro Sclerosi Multipla - Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Elio Scarpini
2016

Centro SM - Ambulatorio Malattie Demielinizzanti Ospedale di Circolo e Fondazione Macchi
Paola Banfi
2015

Centro Sclerosi Multipla IRCCS Fondazione Mondino
Roberto Bergamaschi
2015

Centro ad Alta Specializzazione per la diagnosi e la cura della Sclerosi Multipla - Ospedale Valduce
Raffaella Clerici
2015

Centro Provinciale Sclerosi Multipla ASST Papa Giovanni XXIII
Marta Zaffira Conti
2015

Neuroimmunologia - Centro Provinciale per la diagnosi e terapia della Sclerosi Multipla ASST Crema
Maria Teresa Ferrò
2015

SC Neurologia - ASST Valcamonica Ospedale di Esine
Marinella Turla
2017

Centro SM - ASST Rhodense
Marco Ronzoni
2016

Centro Sclerosi Multipla - Divisione di Neurologia - Azienda Ospedaliera A. Manzoni
Roberto Balgera
2015

Dipartimento di Neuroscienze Pediatriche Fondazione IRCCS Istituto Neurologico C. Besta
Alessandra Tozzo
2020

Centro Sclerosi Multipla - UO Neurologia ASST Fatebenefratelli Sacco - PO Luigi Sacco
Pierluigi Bertora
2015

UO Neurologia - Ospedale Maggiore
Silvia Fermi
2018

Centro Sclerosi Multipla - Ospedale San Carlo ASST Santi Paolo e Carlo
Giuseppe Santuccio
2015

IRCCS Fondazione Mondino UO Neuropsichiatria infantile
Angela Berardinelli
2020

Centro SM UO Neurologia ASST Lariana Ospedale S. Anna
Nerina Mascoli
2015

Centro Sclerosi Multipla - Unità di Neurologia IRCCS Ospedale San Raffaele
Massimo Filippi
2016

Azienza Socio Sanitaria Territoriale (ASST) della Valtellina e Alto Lario - Sedi di Sondrio e Sondalo - Reparto di Neurologia
Alessandro Leone
2015

Centro Sclerosi Multipla Casa di Cura Igea
Giancarlo Comi
2022

Istituto Clinico Humanitas - HUNIMED
Giuseppe Liberatore
2022

MARCHE

Clinica Neurologica - AOU delle
Raffaella Cerqua
2015

Ambulatorio Sclerosi Multipla - UO di Neurologia AV5 Ospedale Civile Madonna del Soccorso
Cristina Paci
2015

Ambulatorio Sclerosi Multipla - UO Neurologia AV5 Ospedale C. e G. Mazzoni
Gabriella Cacchiò
2015

Centro Sclerosi Multipla - c/o UOC Neurologia Ospedale di Macerata
Elisabetta Cartechini
2015

UOC Neurologia - Ospedale Civile di Senigallia
Giorgia Jorio
2024

UO Neurologia, Azienda Ospedaliera Marche Nord, Centro SM
Cristiana Taus
2022

MOLISE

Centro Sclerosi Multipla - IRCCS Neuromed
Paolo Bellantonio
2015

PIEMONTE

Divisione di Neurologia - Ospedale Civile
Carlotta Chiavazza
2022

Centro Sclerosi Multipla - SC Neurologia AO S. Croce e Carle
Marco Capobianco
2015

Centro SM - Ospedale Regina Montis Regalis
Gabriella Turano
2017

Centro Sclerosi Multipla - Clinica Neurologica Dipartimento di Medicina Traslazionale Università del Piemonte Orientale
Roberto Cantello
2017

Dipartimento di Riabilitazione CRRF Mons. Luigi Novarese
Claudio Solaro
2018

Centro SM ASL CN2 Alba-Bra
Sara Giacone
2023

Centro Sclerosi Multipla - Divisione di Neurologia Ospedale Maria Vittoria
Daniele Imperiale
2016

Centro di riferimento Regionale SM (CRESM) SCDO Neurologia - AOU San Luigi Gonzaga
Alessia Di Sapio
2015

Divisione di Neurologia - Ospedale Martini
Valeria Studer
2023

Divisione di Neurologia - Ospedale SS. Annunziata
Maria Roberta Bongioanni
2023

Istituto Auxologico Italiano IRCCS Istituto Scientifico Ospedale S. Giuseppe e Ambulatorio
Andrea Mauro Brioschi
2017

Servizio Universitario Sclerosi Multipla Dip. di Neuroscienze Rita Levi Montalcini dell'Università di Torino - Unità Operativa Complessa Neurologia 2 dell'AOU Città della Salute e della Scienza di Torino
Marco Bozzali
2020

Centro Sclerosi Multipla - Divisione Di Neurologia Ospedale Civile - ASL 4
Giulia De Rosa
2015

AOU SS Antonio e Biagio e Cesare Arrigo
Francesco Passantino
2018

ASLTO4 - Neurologia - Ospedale di Chivasso
Claudio Geda
2015

Centro Clinico delle Malattie Demielinizzanti dell'ASL di Biella - Ospedale degli Infermi
Lorenzo Capone
2015

Struttura Complessa a Direzione Ospedaliera (SCDO) Neurologia 1 - AOU San Luigi Gonzaga
Marinella Clerico
2015

Dipartimento di Scienza della Sanità Pubblica e Pediatriche SCDU Neuropsichiatria Infantile AO Città della Salute e della Scienza della Città di Torino Presidio Ospedale Infantile Regina Margherita
Carlotta Canavese
2022

Centro SM - Neurologia 1U - AOU Città della Salute e della Scienza di Torino
Paola Cavalla
2017

PUGLIA

Centro SM - DiBraiN - Dipartimento di Biomedicina Traslazionale e Neuroscienze - Università di Bari
Pietro Iaffaldano
2017

Divisione di Neurologia - Ospedale Vito Fazzi
Francesca De Robertis
2017

Centro Sclerosi Multipla - UOC Neurologia Ospedale A. Perrino
Augusto Rini
2015

Centro SM c/o UO di Neurologia - PO Dimiccoli
Imma Plasmati
2015

Centro Malattie Demielinizzanti Ospedale Generale Regionale F. Miulli
Maurizia Gatto
2015

Ospedale Civile Di Venere
Mariangela D'Onghia
2021

Centro Interdipartimentale per le Malattie Demielinizzanti - SC Neurologia Universitaria AOU Policlinico Foggia
Carlo Avolio
2015

Centro Sclerosi Multipla - UOC di Neurologia Giulio Coppola - Ospedale Civile F. Ferrari
Roberto De Masi
2023

Divisione di Neurologia - Ospedale SS Annunziata
Rossana Sgobio
2022

Centro Sclerosi Multipla UOC di Neurologia Ospedale Della Murgia Fabio Perinei
Ardito Bonaventura
2015

UOC Neuropsichiatria Infantile Universitaria Policlinico di Bari
Marta Simone
2020

Centro SM UO Neurologia - Fondazione IRCCS Casa Sollievo della Sofferenza
Maurizio A. Leone
2015

SARDEGNA

Centro Prescrittore Sclerosi Multipla UO di Neurologia - Presidio Ospedaliero di Ozieri - ASL N. 1 Sassari
Antonello Pala
2015

UOC Neuropsichiatria Infantile - AOU di Sassari
Stefano Sotgiu
2020

Centro diagnosi, cura e ricerca per Sclerosi Multipla Ospedale S. Francesco - USL 3
Maria Luisa Piras
2016

Centro Regionale per la diagnosi e la cura della Sclerosi Multipla ASL8 - PO Binaghi
Eleonora Cocco
2016

SS Sclerosi Multipla SC Clinica Neurologica AOU Sassari
Roberto Zarbo
2015

SICILIA

Centro Sclerosi Multipla - c/o UOC di Neurologia AO Papardo
Sonia Milone
2015

Centro Sclerosi Multipla - UOC Neurologia Ospedale Garibaldi Centro
Francesca Matta
2015

Centro Sclerosi Multipla - Ospedale ARNAS Civico Di Cristina Benfratelli
Salvatore Cottone
2020

Divisione di Neurologia - Azienda Ospedaliera S. Elia
Michele Maria Vecchio
2019

UOC Neurologia - Azienda Ospedaliera Cannizzaro
Davide Maimone
2023

Centro Neurolesi Bonino Pulejo IRCCS
Edoardo Sessa
2017

Dipartimento di Radiologia, Diagnostica, Interventistica e Stroke - Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone
Giuseppe Salemi
2015

Centro Sclerosi Multipla - AOU Policlinico Martino
Maria Buccafusca
2015

UOC Neurologia con Stroke Unit Presidio Ospedaliero S. Antonio Abate
Simona Alessi
2024

Fondazione Istituto G. Giglio - Centro SM
Luigi M. E. Grimaldi
2015

Centro Sclerosi Multipla - UOC di Neurologia con Stroke Unit - AOOR Villa Sofia-Cervello
Sabrina Realmuto
2015

Ospedale E. Muscatello
Sebastiano Bucello
2019

UOC di Neuropsichiatria Infantile Centro Regionale Sclerosi Multipla e Malattie Demielinizzanti Ospedale Pediatrico Giovanni Di Cristina dell'Azienda ARNAS Civico - Di Cristina Benfratelli
Giuseppe Santangelo
2017

SC Provinciale di Neurologia - ASP Ragusa PO R. Guzzardi
Antonello Giordano
2015

Centro Sclerosi Multipla - AOL Policlinico Vittorio Emanuele - Università di Catania
Francesco Patti
2015

UOC di Neuropsichiatria Infantile
Policlinico Universitario G. Martino
Gabriella Di Rosa
2020

TOSCANA

Centro SM PO di Grosseto - Azienda USL Toscana Sud Est - Ospedale Misericordia
Katrin Plewnia
2015

Ambulatorio SM - UOC Clinica Neurologica e Malattie Neurometaboliche - AOU Senese
Nicola De Stefano
2019

Ambulatorio SM - UOSD Neurologia
Ospedale Valdarno S. Maria alla Gruccia
Francesca Rosini
2015

Centro Malattie Demielinizzanti - UO Neurologia
Nuovo Ospedale delle Apuane (NOA)
Isabella Righini
2015

UOC Neurologia e Neurofisiologia Clinica
Università degli Studi di Siena
Monica Ulivelli
2015

Dipartimento NEUROFARBA - Sezione Neuroscienze
Università degli Studi di Firenze - Centro SM SODc Riabilitazione Neurologica - AOU Careggi
Maria Pia Amato
2015

Centro Aziendale SM - UO Neurologia
Ospedale S. Donato
Benedetta Calchetti
2020

Ospedale di Prato - Centro per la Sclerosi Multipla
Unità Operativa di Neurologia
Mario Falcini
2015

Ambulatorio Sclerosi Multipla - Unità Operativa di Neurologia e Neurofisiopatologia - Spedali Riuniti
Cristina Fioretti
2015

Centro Malattie Disimmuni del SNC e SNP
Ospedale San Luca
Patrizia Alessandra Maritato
2024

Ambulatorio Malattie Demielinizzanti
UOC Neurologia - Ospedale Lotti
Chiara Pecori
2015

UOC Neurologia Pediatrica AOU Meyer
Federico Melani
2020

Centro di Riferimento Regionale per il Trattamento della Sclerosi Multipla - SOD Neurologia II
AOU Careggi
Luca Massacesi
2020

Ospedale San Jacopo - Ambulatorio Malattie Demielinizzanti - Divisione Neurologia
Anna Luisa Ancona
2020

UO Neurologia - Ospedale S. Giuseppe
Maria Letizia Bartolozzi
2023

Centro Malattie Demielinizzanti UO Neurologia
Dipartimento di Medicina Clinica e Sperimentale
Università di Pisa - D.A.I. Neuroscienze AOUP
Livia Pasquali
2015

TRENTINO-ALTO ADIGE/SÜDTIROL

Divisione Neurologia - Az. Spec. Ovest
Ospedale Franz Tappeiner
Francesca Caleri
2022

UMBRIA

Centro Malattie Demielinizzanti UOC Neurologia
USL Umbria 1 Ospedale Città di Castello e Ospedale di Branca
Laura Greco
2024

Centro Malattie Demielinizzanti
Ospedale S. Maria della Misericordia
Paola Sarchielli
2015

Neurologia Centro SM
Ospedale San Giovanni Battista
Francesco Corea
2015

SC di Neurofisiopatologia - AO di Perugia
Maria Grazia Celani
2014

VENETO

Centro SM UOC Neurologia - Ospedale di Santorso, Azienda AULSS 7 - Pedemontana - Regione Veneto

Simona Carella
2022

Fondazione Ospedale San Camillo IRCCS

Cristina Scarpazza
2023

Centro Regionale Specializzato per la Sclerosi Multipla - UOC Neurologia B - Ospedale di Borgo Roma - AOUI Verona

Alberto Gajofatto
2019

Reparto di Neurologia - ULSS 1 Dolomiti Ospedale Santa Maria del Prato

Piero Nicolao
2015

Ambulatorio Sclerosi Multipla e Malattie Demielinizzanti del SNC - UOC di Neurologia Ospedale San Bassiano AULSS7

Alessandro Burlina
2017

Ambulatorio Malattie Demielinizzanti UOC di Neurologia - Ospedale di Conegliano

Marianna Fortunato
2015

Unità di Neurologia - Centro Sclerosi Multipla Ospedale Mater Salutis

Francesco Crescenzo
2022

Ambulatorio Sclerosi Multipla Divisione di Neurologia - Ospedale dell'Angelo

Rocco Quatrale
2016

Centro Sclerosi Multipla - UOC Neurologia Ospedale San Bortolo

Luigi Zuliani
2022

Centro Specializzato Regionale per la Sclerosi Multipla (CeSMuV), Regione Veneto, Dipartimento di Neuroscienze DNS, Azienda Ospedaliera, Università degli Studi di Padova

Paolo Gallo
2015

Centro Sclerosi Multipla - UOC Neurologia Ospedale Ca' Foncello - ULSS2 Marca Trevigiana

Marika Vianello
2015

UOC Neurologia - ULSS2 Marca Trevigiana Ospedale S. Giacomo Apostolo

Bruno Marini
2015