RISM

The Italian Multiple Sclerosis and Related Disorders Register

ITALIAN MULTIPLE SCLEROSIS AND RELATED DISORDERS REGISTER

2025

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

NETWORK OF THE ITALIAN MS CLINICAL CENTERS

SCLEROSI MULTIPLA fondazione italiana

un mondo libero dalla SM

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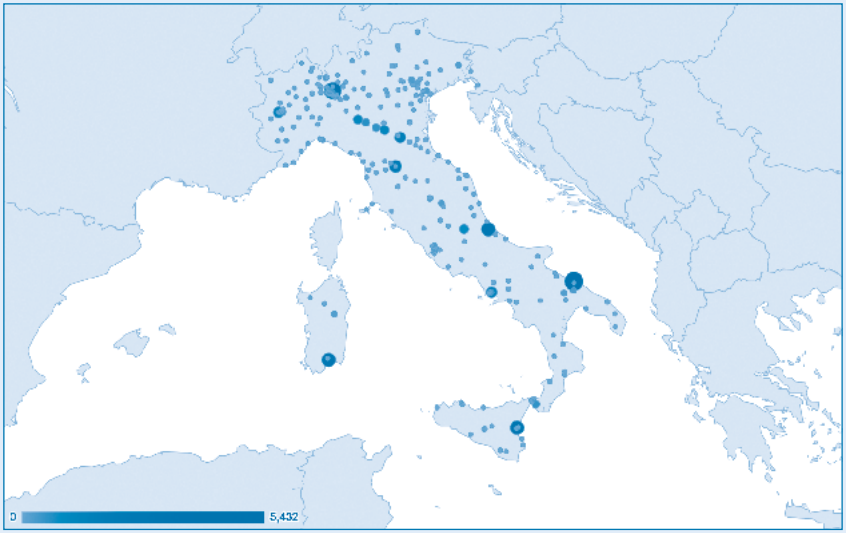
Introduction

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 people with MS followed in the various MS centers in Italy ([1]).

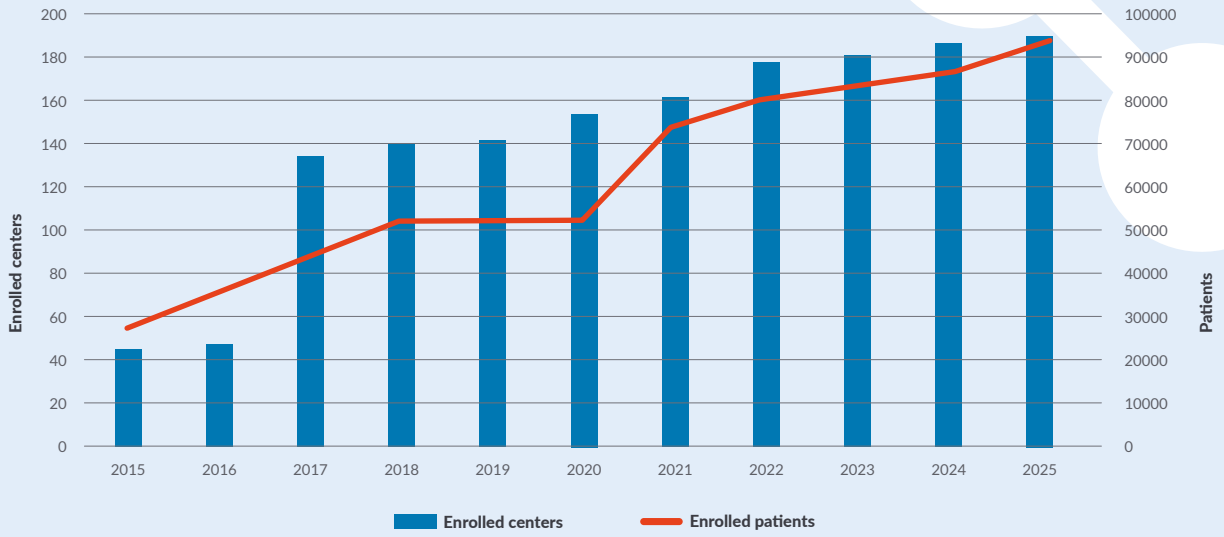


Distribution of patients and clinical multiple sclerosis centers in Italy. The proportional area chart (circles) represents the number of patients for each MS clinical center.

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*

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 from Italian Multiple Sclerosis Register to Italian Multiple Sclerosis and Related Disorders Register. A new module has been included for the collection of information on rare forms of demyelinating diseases: Neuromyelitis Optica Spectrum Disorder (NMOSD) and pathologies associated with the presence of anti-MOG antibodies (MOGAD).
In 2025, RISM marks its 10th year of activity thanks to key strategic aspects of its governance and data quality assurance. Over the past decade, the number of centers has increased to 189 (see appendix 1 for the full list of participating centers), with 19 Italian regions currently represented. RISM has collected the demographic and clinical data from over 95,000 people in care by Italian clinical centers (data updated at July 31st, 2025), starting from the initial 28,000. Variables have expanded from 400 to over 1,400 - now including MRI, pregnancy and COVID-19 modules. Through the transfer system over 3,000 patients have been relocated. A total of 6,050 pediatric onset patients have been recorded, together with 955 NMOSD and MOGAD.
RISM is therefore ready to become a factual 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.



Enrolled centers and patients in the RISM Project from 2015 to 2025

HIGH-PRIORITY AREAS

The Scientific Committee of RISM has identified two high-priority areas:

- **Public Health**: to set up a universal census of patients systematically and continuously updated, in order to obtain accurate estimates of prevalence and incidence of the disease at a 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. Particularly, studies on epidemiology and prognosis, treatment optimization (effectiveness and safety), disease course, early and preclinical/subclinical disease stages (CIS and RIS).

INFRASTRUCTURE ORGANIZATION

EXECUTIVE COMMITTEE
is responsible for the overall direction of the study.

SCIENTIFIC COMMITTEE:
oversees the scientific initiatives.

CENTERS COMMITTEE:
includes the principal investigators of each center.

Observational Studies Expert Committee:
organises training activities for young neurologists; offers consultation activities for ongoing or upcoming studies.

Stakeholder Advisory Board:
involves relevant stakeholders to engage them in the strategic priorities of RISM.

TECHNICAL OPERATIONAL AND COORDINATING STRUCTURE - STOC
is responsible for the technical-operational coordination of the study; deals with the secretarial functions and the coordination of the Research Assistant Network.

Research Assistants Network:
consists of young Research Assistants who have been trained ad hoc to provide local support for the RISM project.

MS Clinical Centers Network: is recognized as the key component of MS care in Italy.

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 (including clinicians, methodologists, and representatives of both MS centers and of the Italian Neurological Society) which oversees the scientific initiatives, promotes specific strategic projects, and approves requests of access to centralized data for further research projects.

The current Executive Committee is composed of:
Maria Trojano, University of Bari representative
MS Center, Department of Translational Biomedicine and Neuroscience (DiBraiN), University of Bari, Bari
Mario Alberto Battaglia, FISM representative
Italian Multiple Sclerosis Foundation - FISM, Genoa

The current Scientific Committee is composed of:
Maria Trojano, Chair
MS Center, Department of Translational Biomedicine and Neuroscience (DiBraiN), University of Bari, Bari
Mario Alberto Battaglia, Co-Chairman
Italian Multiple Sclerosis Foundation - FISM, Genoa
Claudio Gasperini, Representative of the Italian Society of Neurology, ISN
Department of Neuroscience, Azienda Ospedaliera San Camillo-Forlanini, Rome
Eleonora Cocco, Clinical Centers Representative
Regional Center for the Diagnosis and Treatment of Multiple Sclerosis ASL8 P.O. Binaghi, Cagliari, Italy
Matilde Inglese, Clinical Centers Representative
Center for the Study and Treatment of Multiple Sclerosis and Demyelinating Diseases - Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal - Child Sciences, Neurological Clinic - Policlinico San Martino Hospital (DiNOGMI), Genoa
Carla Tortorella, Clinical Center Representative
Multiple Sclerosis Center - Az. Osp. S. Camillo Forlanini, Rome
Paola Mosconi
Italian Multiple Sclerosis Foundation - FISM, Genoa
Marco Capobianco, Secretary
Multiple Sclerosis Center, CS Neurology, AO Santa Croce e Carle, Cuneo
Maria Pia Amato, Expert
Department of NEUROFARBA, University of Florence,
IRCCS Fondazione Don Carlo Gnocchi, Florence
Massimo Filippi, Expert
Neurology Unit and Multiple Sclerosis Center, Neurorehabilitation Unit, Neurophysiology Service, and Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milano, Italy; Vita-Salute San Raffaele University, Milano, Italy

OPERATIONAL STRUCTURE

The Technical Operational and Coordinating Structure, based at FISM in Genoa, operates on behalf of RISM and manages both administrative and technical-operational aspects of the project.

THE STAFF OF THE TECHNICAL OPERATIONAL AND COORDINATING STRUCTURE

Italian Multiple Sclerosis Foundation, Genoa
Coordination: Michela Ponzio, Paola Mosconi, Vito Lepore
Study Coordinators: Marco Salivetto, Pasquale Paletta
RISM Assistant: Sabrina Rutigliano
Legal and Compliance Office: Paolo Bandiera, Laura De Barbieri, Martina Bassi, Lorenzo Garzarelli.

RISM staff members during the celebration of World Multiple Sclerosis Day 2025, Rome

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, a total of 189 MS clinical centers and/or neurology departments have joined the RISM project by signing a mandate, of which 14 are exclusively pediatric centers. Furthermore, 159 clinical centers are actively collecting and updating data of MS and RD patients.

RESEARCH ASSISTANTS NETWORK

With the aim of increasing the quality of data collection and data entry, a network of research assistants (RAs) has been *ad hoc* trained. Currently, 23 RAs are active in 15 Italian Regions (following approximately 130 centers) and are allocated to one or more centers according to centers' contribution to the project in terms of number of patients enrolled and their geographic distribution. RAs activities include: supporting the start-up phase of the project at MS centers, supporting the on-time implementation of the project at MS centers, and ensuring a standardized data collection and management.

LIST OF ACTIVE RESEARCH ASSISTANTS

Italian Multiple Sclerosis Foundation, Genoa

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

Junior staff: Alessandra Del Prete, Teresa Fonsdituri, Agata Marchese, Martina Marciano, Silvia Marinetto, Chiara Monetti, Rosanna Petrillo, Valentina Tallarico, Stefania Treccarichi, Eliana Zaccone.

Agata Marchese

Antonino Rallo

Beatrice Biolzi

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Daniele Dell'Anna

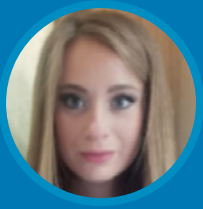
Eliana Zaccone

Federica Martini

Giovanna R. Piredda

Ilaria Maietta

Ilaria Rossi



Martina Marciano

Monica Romoli

Ornella Moreggia

Alessandra Del Prete

Silvia Marinetto

Silvia Perugini

Sonia Di Lemme

Stefania Treccarichi

Chiara Raimondi

Teresa Fonsdituri

Valentina Tallarico

The network of 23 Research Assistants, July 2025

STAKEHOLDER ADVISORY BOARD

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.

OBSERVATIONAL STUDIES EXPERTS COMMITTEE

This committee was established in 2024 and is composed of six neurologists and three statisticians with the following responsibilities:

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

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

CURRENT OBSERVATIONAL STUDIES EXPERTS COMMITTEE

Copetti Massimiliano (statistician)
Head of Unit of Biostatistics, I.R.C.C.S. Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Foggia
Lucisano Giuseppe (statistician)
Department of Basic Medical Sciences, MS Center, Department of Translational Biomedicine and Neuroscience (DiBraiN), University of Bari, Bari
Santucci Claudia (statistician)
Department of Clinical and Community Sciences, University of Milan
Ferraro Diana (neurologist)
Centro dell'Ospedale Civile di Baggiovara, Azienda Ospedaliero-Universitaria di Modena Sclerosi Multipla
Iaffaldano Pietro (neurologist)
University of Bari Aldo Moro, Department of Biomedicine Translational and Neuroscience "DiBraiN" Multiple Sclerosis Center, Bari
Lorefice Lorena (neurologist)
Centro Sclerosi Multipla Ospedale Binaghi, Cagliari
Portaccio Emilio (neurologist)
Department of NEUROFARBA, University of Florence, Florence

Current Members of the Observational Studies Experts Committee

Massimiliano Copetti

Giuseppe Lucisano

Claudia Santucci

Pietro Iaffaldano

Diana Ferraro

Lorena Lorefice

Mara Rocca

Emilio Portaccio

Luca Prosperini

Roberto Bergamaschi

Matteo Foschi

Giorgia Teresa Maniscalco

Elisabetta Signoriello

Current Consultants of the Observational Studies Experts Committee

Prosperini Luca (neurologist)
U.O.C. Neurologia e Neurofisiopatologia, A.O. S. Camillo-Forlanini, Roma
Rocca Maria Assunta (neurologist)
San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan

CONSULTANTS:

Bergamaschi Roberto (Multiple Sclerosis Center, IRCCS Mondino Foundation); **Foschi Matteo** (Dipartimento di Neuroscienze, Centro SM e Malattie Neurodegenerative - U.O.C. Neurologia, Ospedale S. Maria delle Croci, AUSL Romagna, Ravenna); **Maniscalco Giorgia Teresa** (Centro Regionale di Diagnosi e Terapia della Sclerosi Multipla); **Signoriello Elisabetta** (Centro Clinico per la Sclerosi Multipla - II Clinica Neurologica - II Università di Napoli).

HIGHLIGHTS FROM 2022-2025

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
- "A data-driven future to cure MS and related disorders", Session dedicated to RISM| Rome, 29 May 2025

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 Operational and Coordinating Structure 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.

Rita Levi Montalcini Award to Pietro Iaffaldano
FISM Congress 2025

The Annual Big Multiple Sclerosis
Data Network meeting | 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. 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 Annual Big Multiple Sclerosis
Data Network meeting | Copenaghen, 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 | 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.

Joint event: The Big Multiple Sclerosis Data Network meeting and the 3rd BigMS Statistical Workshop | Matera, 18-20 September 2025

A joint event was held in Matera, Italy, from 18 to 20 September 2025. On 18 and 19 September, the BMSD Annual Meeting brought together members of the registry network to discuss the latest updates. The agenda included the presentation of documents submitted by BMSD to the EMA as part of the Qualification Opinion application, as well as discussions on opportunities to expand the Network. Key topics included criteria for the inclusion of new registries and the collection of specific data, such as those related to NMOSD, MOGAD, and Patient-Reported Outcomes (PROs). A dedicated session focused on proposals for new academic projects to be conducted within the Network.

On 19 and 20 September, the BMSD Statistical Workshop took place, entitled "Advanced Statistical Methods for Observational Studies in MS." The workshop covered key statistical approaches for handling multi-source real-world data, strategies for integrating different MS data sources for research purposes, and the development of predictive models for real-world applications.

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
- The 41st ECTRIMS Congress in Barcelona | 24-26 September 2025

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
- Padua | 24-28 October 2025 (upcoming)

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 2025 Meeting in Padua, the election of the three new MS centers representatives for the RISM Scientific Committee will take place.

Training course titled: "Observational studies conducted using data collected by the Italian Multiple Sclerosis and Related Disorders Register", 2025

A training event organized by the Observational Studies Experts Committee is currently underway and is aimed at young neurologists and statisticians seeking to strengthen their skills in the design, execution, and analysis of observational studies using data from RISM. The course's objective is to prepare a new generation of researchers capable of fully harnessing the potential of RISM to conduct high-quality observational research.

Observational studies conducted using data collected by the italian registerms and related diseases

4 WEBINAR EVENT

- ➡ Alignment and Introduction to the RISM
- ➡ Pratical analysis of data from the RISM
- ➡ Study designs of observational research
- ➡ Advanced statistical methodology

1 RESIDENTIAL EVENT

- ➡ Generating a research project

Dedicated Software

During the first years, RISM used a client–server solution software, an offline computerized medical folder that needed a periodic upload by clinical centers. At the end of 2016, a new web-based software named the RISM-App was developed. From April 2021, RISM is exclusively running on this new modular web-based software, currently at its 3.14 release. The software access happens via the reserved area of the website of the project (https://www.registroitalianosm.it/).

FEATURES 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 subjects produces a significant improvement in the pooling of the data in the central database.
- **Practical**: data entry is possible through different devices (PC, mobile, tablet).
- **Secure**: 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.
- **Easily accessible**: an internet access is sufficient. A Privacy Impact Assessment has been evaluated to assess the security level of the website.
- **Standardized**: the database uses standardized coding databases, such as MedDRA, ICD9CM, Eurocat and Farmadati. A Standard Operating Procedures manual is periodically updated to standardize data collection and RISM-App utilization (last update May 2025).
- **Printable**: it is possible to print a report containing patients' 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 adult onset patient, and other variables included in specific modules such as:

Drugs

This section is dedicated to the patient's treatment history, considering both DMTs and non-specific drugs. This module includes the risk-management plan for all the Disease Modifying Therapies (Adverse Events and Serious Adverse Events are coded through MedDRA; Comorbidities are coded through 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 Examinations

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

COVID-19

This section collects information about the SARS-CoV-2 infection such as: diagnosis, severity, outcome and correlation with DMTs and vaccinations.

Pregnancy

This section collects information regarding pregnancy, maternal and fetal outcomes of women with MS and their children.

Medical history and risk factors

This section collects information about comorbidities and the familiar clinical history.

Evaluation, tests and scales

This section collects information about cognitive, motor and quality of life domains.

MS Pediatric Onset

This section collects information on people with a pediatric onset. This module includes additional information respect to the adult cases, such as environmental risk factors, vaccinations, cognitive functioning over time and specific MRI features.

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). This module may collect information from both adult and pediatric onset subjects, and additional information respect to the MS cases are collected, such as specific information on symptoms at onset, relapses and MRI.

DATA MONITORING

Data are centrally monitored in order to guarantee the high quality of the information collected. Several quality control tools have been implemented in order to increase the quality and generalizability of the data collected. Centers are periodically contacted with ad hoc reports with queries on the missing data or inconsistencies among the variables collected.
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

Every 2 months, RAs receive an update on the progress of the centers they are in charge of and share it with principal investigators of the participating center. Each center receives a monthly communication with updates and clarifications regarding data entry and procedures pertaining to the project.

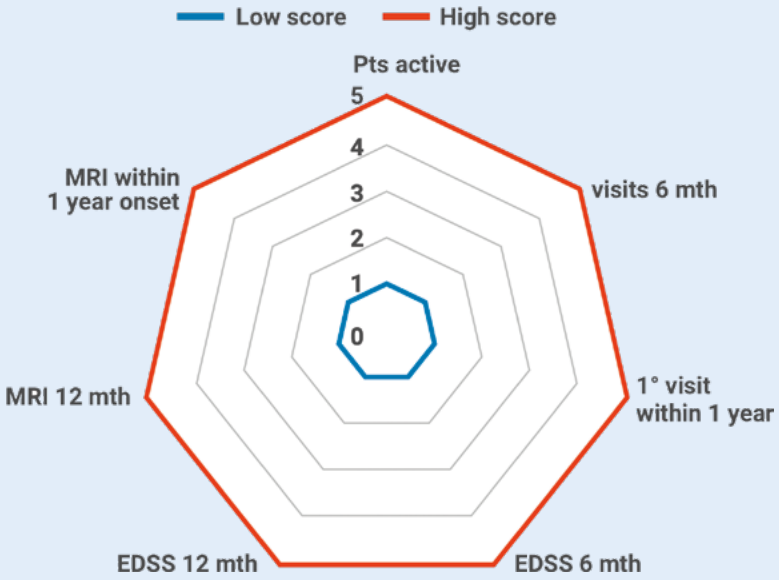
Based on our previous published experience ([2]), an *ad hoc* working group was established and reviewed the previous set of indicators with the aim to improve the quality, completeness, timeliness, generalization, and representativeness of the collected data.

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.*

Accordingly, the following indicators were established:

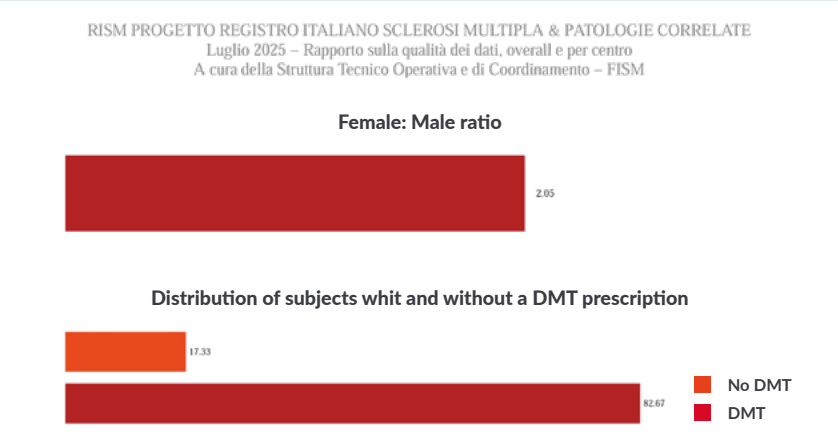
- a set of seven performance indicators reported as radar graph; for each indicator all the centers were awarded with a score of 5 for the best performance, while lower scores from 4 to 1 were attributed for progressively lower performances. (Fig 1a)
- a set of four epidemiological-descriptive indicators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

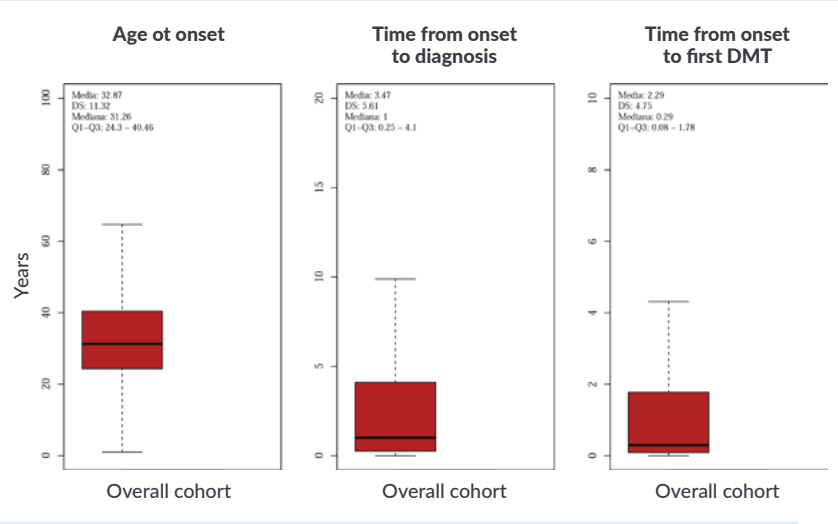
Fig 1a. The seven performance indicators and their graphical representation (radar graph):



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/ follow-up;
5. **EDSS 12 mth:** at least 1 EDSS evaluation every 12 months/ follow-up;
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.

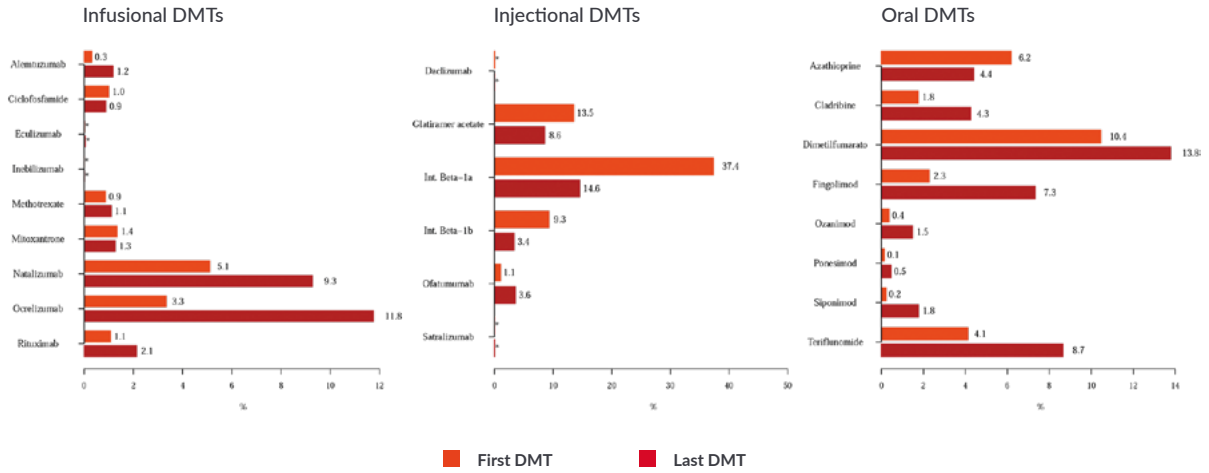
Fig 1b. Set of the four epidemiological-descriptive indicators for the overall RISM cohort.





First and last DMTs distribution by administration route

No.71,850



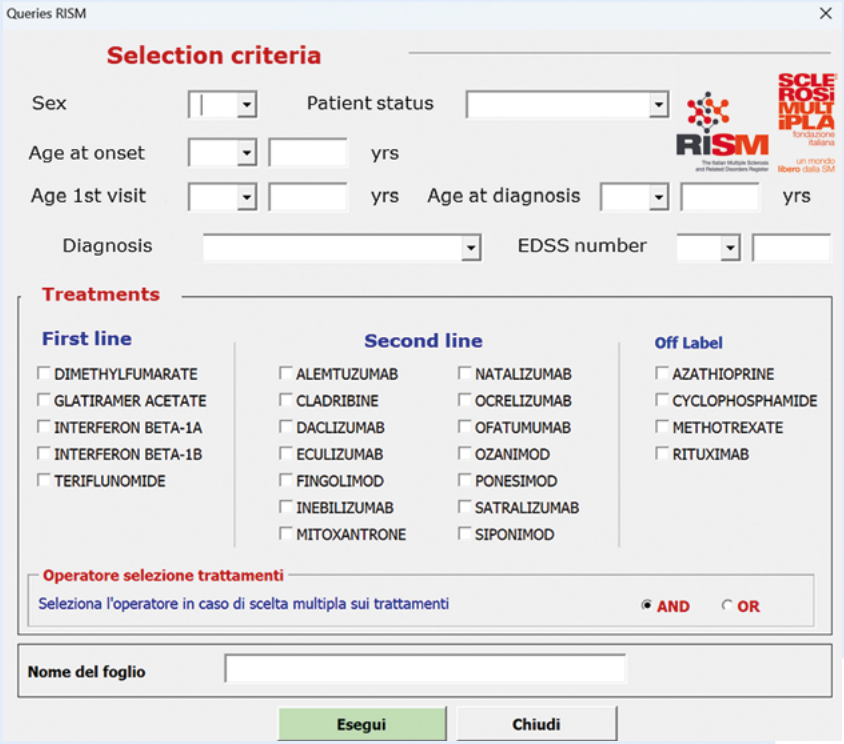
Every six months, each participating center receives a report where their data and performance indicators are bench-marked with the whole sample: in this way, each center can assess its own performances and the level of improvement over time.

Alongside with this work, ad hoc assessments were carried out to monitor data accuracy and consistency:

- potential duplicates were identified in the whole database and checked one by one, fixing the incongruencies and unifying the duplicates. During the last year and a half, a total of 2027 potential duplicates have been identified and solved. In 2024, a system based on the comparisons of critical information from the personal tax-code identifier was implemented in order to avoid the registration of new duplicates.
- over the past two years, targeted assessments of individual cases have been conducted to identify potential data-entry errors related to the recording of treatment information or the occurrence of clinical events.

DEVELOPMENT OF QUERIES FOR THE RISM DATABASE

Despite the ability of each center to download its own data for internal analysis and verification, the complexity of the RISM database and the need for centers to track and analyze their patients longitudinally, required the study and implementation of a query system. This system, launched in 2025, allows center users to quickly, conveniently, and intuitively query their database to perform analyses on their patients, although it will not, however, completely meet the complexity and specificity of analyses for research projects.



RISM queries interface

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 effectiveness and safety of disease-modifying therapies in the general population with MS, including groups of individuals who are excluded from participating in clinical trials (such as elderly or pediatric subjects and individuals with comorbidities). EMA is interested in real-world data regarding the post-marketing drug safety assessment (i.e., Post-Authorization Safety Study—PASS). The RISM project also collaborates on PASS studies. Below, the current active projects are listed:

- MANUSCRIPT study for long-term surveillance of Ocrelizumab treated patients with Multiple Sclerosis (ROCHE)
- CLARION study, for long-term surveillance of oral Cladribine in patients with highly active RMS (MERCK)
- Kesimpta long-term retrospective safety study utilizing real-world data from existing multiple sclerosis registries and databases from multiple countries (NOVARTIS)

Big MS Data Network

BMSD constitutes a network of MS registries working together since 2014 to provide an unparalleled real-world dataset for researchers, marketing authorization holders and regulatory bodies. From January 2025, RISM is responsible for the coordination of the Big MS Data Network.

RISM Staff for BMSD coordination

Chairman BMSD Coordination: Maria Trojano, Honorary Professor of Neurology, University of Bari "Aldo Moro"
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Martina Bassi, Legal Office, Italian Multiple Sclerosis Foundation – FISM
Giuseppe Lucisano, Biostatistician, University of Bari "Aldo Moro"

Maria Trojano, FISM Congress 2025

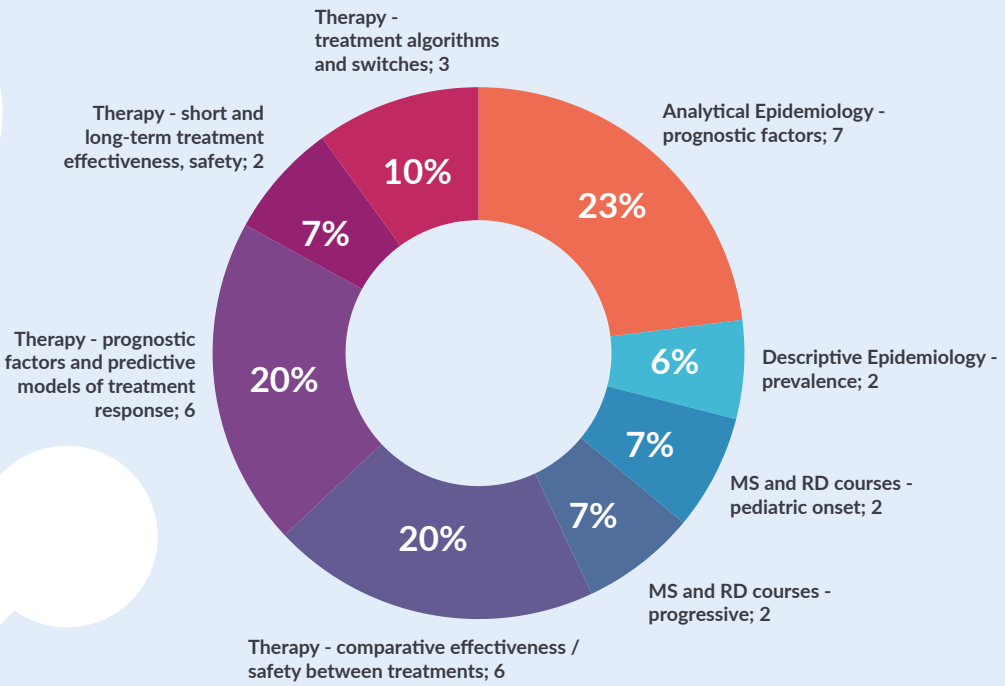
RESEARCH PROJECTS BASED ON THE RISM DATA

Currently 72 projects are approved, 42 are completed and 30 are 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)

To date, more than 50 relevant peer-reviewed publications have been published in international journals.

Main Research Areas of the 30 Ongoing Projects



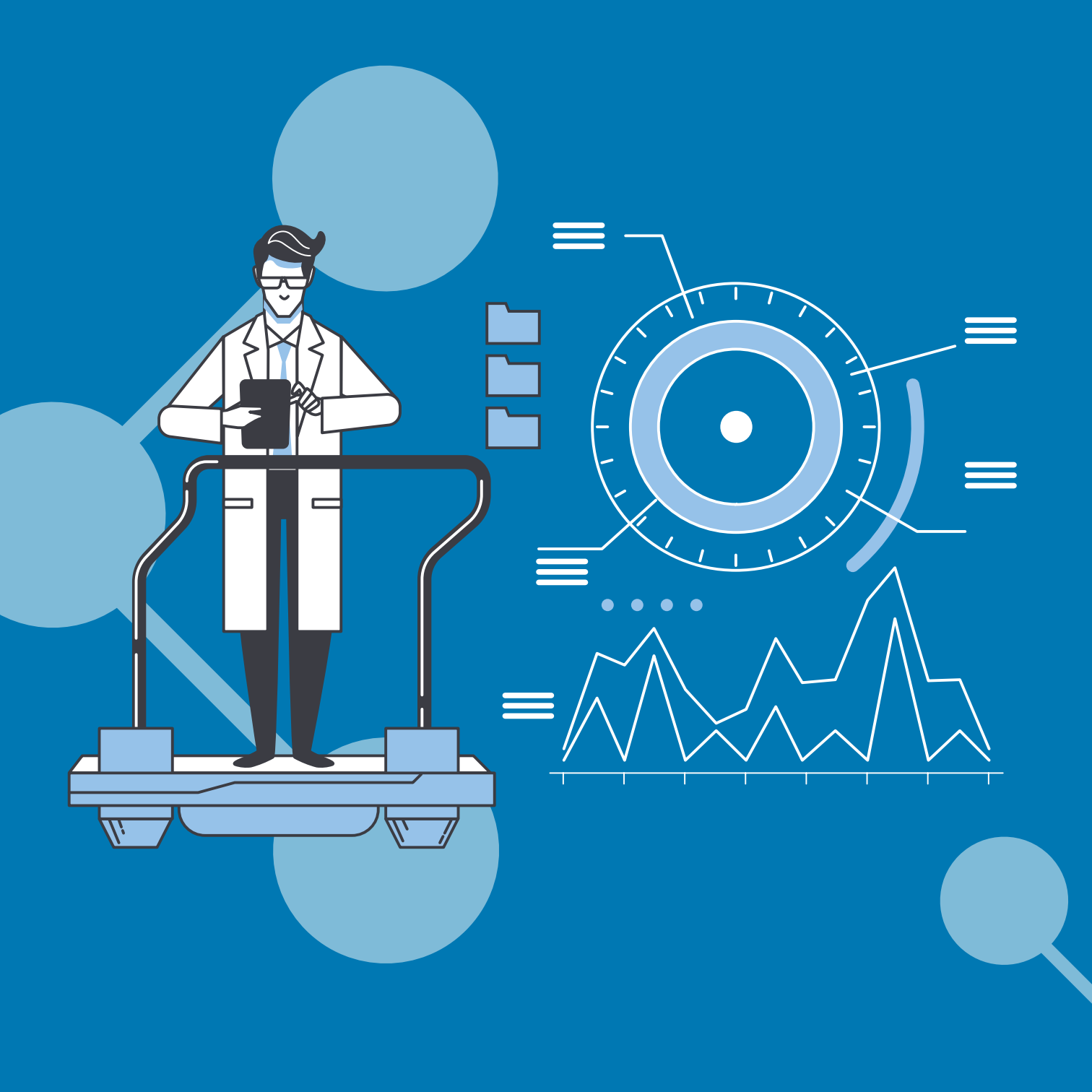
BELOW ARE REPORTED THE TITLES OF 30 ONGOING PROJECTS

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*
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*
Matteo Floris	Pharmacoepidemiological analysis of the Italian Multiple Sclerosis Registry for the design of pharmacogenetic studies of disease modifying therapies	*Descriptive Epidemiology - prevalence*
Francesco Patti	VariaTions in the first-therapeUtic choice in patients with multiple scleRosis across differeNt eras (TURN Study)	*Analytical Epidemiology - prognostic factors*
Maria Trojano	ASsessing long Term effectiveness of OcrelizumAb in ITalian Multiple Sclerosis RegIstry:a cOmparisoN on PIRA and RAW in early vs delaYed treatment	*Analytical Epidemiology - prognostic factors*
Pietro Iaffaldano	Predicting multiple sclerosis disease activity and progression: development of a prognostic score and decisional support system - PROMISING study	*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*
Selene Diamant	Impact of Tenofovir treatment on the course of Multiple Sclerosis in patients with chronic HBV infection	*Analytical Epidemiology - prognostic factors*
Luca Prosperini	Educational attainment and long-term disability milestones in multiple sclerosis: cognitive reserve or health literacy?	*Analytical Epidemiology - prognostic factors*

Alessia Fiore	Effectiveness of cell-depleting versus immunosequestering DMTs in preventing relapses during pregnancy and post-partum in women with Multiple Sclerosis	*Therapy - comparative effectiveness / safety between treatments*
Francesco Patti	Efficacy and Safety of Fingolimod, Ozanimod, and Ponesimod Comparative efficacy and safety Using propensity Score matching (FOCUS study)	*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	*Therapy - comparative effectiveness / safety between treatments*
Tomas Kalincik	Timing and comparative effectiveness of high-efficacy disease-modifying therapies in childhood-onset multiple sclerosis	*Therapy - comparative effectiveness / safety between treatments*
Aurora Zanghì	Fingolimod Exit strategy: a real word Italian registry study	*Therapy - comparative effectiveness / safety between treatments*
Tomas Kalincik	Treatment de-escalation and cessation after cell trafficking agents in MS patients older than 60 years	*Therapy - treatment algorithms and switches*
Melinda Magyari	De-escalation of High-Efficacy Disease-Modifying Therapy Compared to Continuation or Discontinuation in Patients Older than 50 Years with Non-Active Multiple Sclerosis	*Therapy - treatment algorithms and switches*
Massimo Filippi	Discontinuation of therapy in Multiple Sclerosis: predictive factors of disease stability after withdrawal of Disease Modifying Drugs	*Therapy - treatment algorithms and switches*
Giuseppe Schirò	Risk of progression independent of relapse activity following cladribine treatment in people with relapsing multiple sclerosis: a retrospective five years multicentric study	*Therapy - prognostic factors and predictive models of treatment response*
Massimo Filippi	Predictors of response to cladribine in multiple sclerosis patients	*Therapy - prognostic factors and predictive models of treatment response*
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*
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*
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*
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, safety*
Emanuele D'Amico	Stop or not the disease-modifying therapies in secondary progressive multiple sclerosis: a comparison study of disability accrual trajectory	*Therapy - short and long-term treatment effectiveness, safety*
Luigi Maria Edoardo Grimaldi	A search for neurological effects of Semaglutide and other anti-diabetic drugs in people with multiple sclerosis and diabetes	*Therapy - short and long-term treatment effectiveness, safety*
David Laplaud	TARgeting Treatment Optimization in Pediatric Onset Multiple Sclerosis (TARTOPOMS).	*MS and RD courses - pediatric onset*
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 - progressive*
Luca Massacesi	Comparative effectiveness of IV cyclophosphamide therapy versus no- or siponimod-treatment in delaying disability accrual in Secondary Progressive Multiple Sclerosis.	*MS and RD courses - progressive*
Mattia Pozzato	"HIGH-EFFECT-POMS vs AOMS - Impact of high-efficacy disease modifying treatments in pediatric-onset multiple sclerosis patients compared to adult-onset: a study from the Italian Multiple Sclerosis Registry"	*MS and RD courses-pediatric onset*

THE MOST RELEVANT PUBLICATIONS



Early Intensive Versus Escalation Approach: Ten-Year Impact on Disability in Relapsing Multiple Sclerosis

REFERENCE

Iaffaldano P, Lucisano G, Guerra T, Caputo F, Simone M, Copetti M, Paolicelli D, Portaccio E, Patti F, Perini P, Brescia Morra V, Di Sapio A, Inglese M, Pozzilli C, Lus G, Salemi G, Curti E, De Luca G, Valentino P, Cocco E, Cavalla P, Avolio C, Lugaresi A, Gallo A, Annovazzi P, Rocca MA, Chisari CG, Filippi M, Amato MP, Trojano M; Italian MS Register. *Early Intensive Versus Escalation Approach: Ten-Year Impact on Disability in Relapsing Multiple Sclerosis.* **Ann Clin Transl Neurol. 2025** Jul 6. doi: 10.1002/acn3.70131

OBJECTIVE

To evaluate the long-term impact of early intensive treatment (EIT) versus escalation (ESC) strategies using high-efficacy disease-modifying therapies (HE-DMTs) on disability progression in relapsing multiple sclerosis (RMS).

METHODS

This observational study included 4,878 RMS patients from the Italian Multiple Sclerosis Register. Eligible participants initiated their first disease-modifying therapy (DMT) within 3 years of disease onset and had ≥ 5 years of follow-up with at least three Expanded Disability Status Scale (EDSS) evaluations. Patients were categorized into the EIT group if they started with HE-DMTs and into the ESC group if HE-DMTs were initiated after ≥ 1 year of moderate-efficacy therapy. Propensity score matching was performed to balance baseline

characteristics. Outcomes included disability trajectories assessed using linear mixed models for repeated measures and risks of confirmed disability accrual (CDA), progression independent of relapse activity (PIRA), and relapse-associated worsening (RAW) evaluated using Cox proportional hazards models.

RESULTS

Post-matching analysis of 908 pairs revealed significantly slower disability progression in the EIT group compared to the ESC group. At 10 years, the delta-EDSS difference between groups was -0.63 (95% CI: -0.83 to -0.43; $p < 0.0001$). ESC was associated with higher risks of CDA (HR 1.36, 95% CI: 1.20-1.54; $p < 0.0001$), PIRA (HR 1.22, 95% CI: 1.05-1.40; $p = 0.0074$), and RAW (HR 1.55, 95% CI: 1.17-2.05; $p = 0.0021$).

INTERPRETATION

EIT significantly reduces long-term disability progression in RMS compared to ESC. These findings underscore the potential of EIT to optimize long-term outcomes in RMS patients.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENT

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

PRINCIPAL INVESTIGATOR:

Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

Age-dependent response to initial highly effective treatment in relapsing multiple sclerosis

REFERENCE

Portaccio E, Betti M, De Meo E, Pastò L, Razzolini L, Patti F, Brescia Morra V, De Luca G, Pozzilli C, Tortorella C, Cocco E, Salemi G, Ferraro D, Vianello M, Lus G, Lugaresi A, Inglese M, Tedeschi G, Montepietra S, Di Sapio A, Zaffaroni M, Iaffaldano P, Simone M, Filippi M, Trojano M, Amato MP. *Age-dependent response to initial highly effective treatment in relapsing multiple sclerosis.* **Mult Scler. 2025** Jul;31(8):985-994. doi: 10.1177/13524585251345317

OBJECTIVE

To assess the impact of age on the superiority of highly effective (HE) disease-modifying treatments (DMTs) compared to platform DMTs in a real-world population of relapsing MS patients (pwMS).

METHODS

A total of 20,984 pwMS were extracted from the Italian Multiple Sclerosis Register with a diagnosis of Clinically Isolated Syndrome or Relapsing-Remitting MS, at least four Expanded Disability Status Scale (EDSS) evaluations and 2 years follow-up, starting DMT. The baseline was the nearest visit to the first DMT starting date. The risk of first 24-week confirmed disability accumulation (CDA) on EDSS in HE versus platform DMTs after 2 years and the entire follow-up was assessed through Cox regression models.

RESULTS

After 1:1 propensity score matching, we evaluated 1,698 pwMS initiating HE-DMTs and 1698 initiating platforms. After 2 years follow-up, the proportion of CDA events was lower in patients on HE-DMTs (12.2%) than those on platform DMTs (15%), as confirmed by Cox regression analysis (hazard ratio (HR) = 0.22, 95% confidence interval (CI) = 0.10–0.47; $p < 0.001$). HE-DMTs were more effective in patients under 45 years of age (HR = 0.49, 95% CI = 0.39–0.63; $p < 0.001$), but not in patients over 45 (HR = 0.77, 95% CI = 0.54–1.08, $p = 0.125$). Notably, prolonged exposure to any DMT during follow-up reduced disability accumulation even in patients over 45 (HR = 0.13, 95% CI = 0.02–0.99; $p = 0.050$).

CONCLUSION

This real-world study of relapsing pwMS demonstrates that the benefit of initial HE treatment diminishes with age. However, even in older patients, DMT exposure, regardless of the efficacy level, appears to reduce disability accumulation, and so, on an individual level, initial HE treatment could still be more effective.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - PROGNOSTIC FACTORS AND PREDICTIVE MODELS OF TREATMENT RESPONSE

TITLE: **Evaluating Age-Dependent Efficacy of Multiple Sclerosis Treatments in a Real-Life Cohort**

PRINCIPAL INVESTIGATOR:
Maria Pia Amato, Dipartimento NEUROFARBA, Divisione di Riabilitazione Neurologica, Azienda Ospedaliero- Universitaria Careggi; IRCCS Fondazione Don Carlo Gnocchi, Firenze, Italia

Multiple sclerosis from onset to secondary progression: a 30-year Italian register study

REFERENCE

Zanghì A, Copetti M, Avolio C, Paolicelli D, Romeo MAL, Patti F, De Luca G, Amato MP, Galgani S, Sola P, Salemi G, Gallo P, Granella F, Romano S, Zaffaroni M, Bergamaschi R, Pozzilli C, Lus G, Vianello M, Trojano M, D'Amico E; Italian Multiple Sclerosis register. *Multiple sclerosis from onset to secondary progression: a 30-year Italian register study*. **J Neurol Neurosurg Psychiatry. 2025** Jun 15:jnnp-2025-335958. doi: 10.1136/jnnp-2025-335958

BACKGROUND

Three decades have passed since the initial approval of disease-modifying therapies (DMTs). Ongoing discussion is focused on fundamental aspects of the disease, highlighting a growing division between successes in managing relapsing multiple sclerosis (MS) and the persistent challenges posed by disease progression.

METHODS

A cohort study on prospectively acquired data from the Italian MS register. The primary outcome was to describe the MS disease course from onset to secondary progression (SP) defined according to a data-driven algorithm over 30 years follow-up and according to five different eras of disease onset.

RESULTS

A total cohort of 9,958 patients was analysed; 1,364 converted to SP after a mean of 8.5 (SD 5.5) years. A higher rate of patients converting to SP had never been exposed to DMTs (135, 9.9% vs 424, 5.2%) than non-converting ones. The treatment coverage was also lower in patients converting to SP than non-converting ones 58.4 (SD 31.5) vs 73.6 (SD 27.6). The SP incidence rate was 1.26 (95% CI 1.19 to 1.32) overall. The rates showed a downward trend among the different eras: from 1st era 1.98 (95% CI 1.73 to 2.27) to 5th era 1.15 (95% CI 0.97 to 1.35). In the multivariable Cox model, 10% increase of treatment coverage was associated to 19% lower risk to convert to SP (10%, HR 0.89, 95% CI 0.87 to 0.90).

CONCLUSIONS

This 30-year analysis suggests that SP conversion rates have decreased over time, partially explained by improvements in therapeutic coverage. Future research should adopt a multifaceted approach to develop more comprehensive models of disease progression.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS, SAFETY

TITLE: **Stop or not the disease-modifying therapies in secondary progressive multiple sclerosis: a comparison study of disability accrual trajectory**

PRINCIPAL INVESTIGATOR:
Emanuele D'Amico, Dipartimento Di Scienze Mediche, Chirurgiche e Tecnologie Avanzate, Università degli Studi di Catania, Catania, Italia

The Italian Multiple Sclerosis Register Experience With Cladribine: Impact on Relapses, PIRA, and Treatment Sequencing Strategies Evaluation

REFERENCE

Guerra T, Copetti M, Zanetta C, Patti F, Chisari CG, Barbuti E, Portaccio E, Foschi M, Conte A, Ferraro D, Cocco EE, Fantozzi R, Maniscalco GT, Salemi G, Tortorella C, Paolicelli D, Filippi M, Amato MP, Trojano M, Iaffaldano P; Italian Multiple Sclerosis & Related Disorders Register (RISM). *The* Italian Multiple Sclerosis Register *Experience With Cladribine: Impact on Relapses, PIRA, and Treatment Sequencing Strategies Evaluation.* **Neurol Neuroimmunol Neuroinflamm. 2025** Jul;12(4):e200415. doi: 10.1212/NXI.0000000000200415

BACKGROUND AND OBJECTIVES

Cladribine is an immune reconstitution therapy approved for relapsing multiple sclerosis (RMS). This multicentric retrospective study of the Italian Multiple Sclerosis Register (RISM) aimed to assess the effect of cladribine on the annualized relapse rate (ARR) and progression independent of relapse activity (PIRA) phenomena, also evaluating the strategies of disease-modifying treatment (DMT) continuation after cladribine termination.

METHODS

Patients with RMS treated with at least one cycle of cladribine recorded in RISM after 2018 were retrospectively included in the analysis. Patients previously treated with other DMTs were stratified into moderately and highly effective DMTs. Adjusted ARR and PIRA events were calculated in the overall cohort and

stratified by age at cladribine start (<50 vs ≥ 50 years) and by previous DMT. ARRs were compared between groups using negative binomial models. PIRA was analyzed using the Ghosh-Lin Cox-type regression for the marginal mean. DMTs prescribed after cladribine cycles were analyzed.

RESULTS

A total of 2,329 patients treated with cladribine were identified in RISM, with a median (IQR) age of 36.5 (29.2–45.2) years at treatment start. 1,488 patients (63.9%) received 2 courses of cladribine. ARR decreased ($p < 0.0001$) from 0.96 (95% CI 0.91–1.02) in the 2 years preceding cladribine start to 0.09 (0.08–0.11) during the 2 years after in the overall cohort. One hundred thirty-three PIRA events were reported during the noncladribine treatment period and 54 during cladribine therapy (HR 0.711, 95% CI 0.531–0.952, $p = 0.0219$) in the entire cohort. All the analyses stratified by age and previous treatment confirmed the significant reduction in PIRA events and the suppression of relapse activity. After cladribine, most DMTs prescribed were ocrelizumab, ofatumumab, and natalizumab. Eight patients re-treated with an additional cycle of cladribine were also identified.

DISCUSSION

For patients with RMS, both naïve and switchers, as well as younger and older patients, cladribine is an effective treatment in reducing relapses and PIRA. Different therapeutic strategies after cladribine are currently reported.

CLASSIFICATION OF EVIDENCE

This study provides Class IV evidence that for patients with relapsing multiple sclerosis, cladribine treatment is associated with a reduction in ARR and PIRA events.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - PROGNOSTIC FACTORS AND PREDICTIVE MODELS OF TREATMENT RESPONSE

TITLE: **Assessment of cladribine therapy over time: effectiveness, safety and evaluation of treatment sequencing beyond year four**

PRINCIPAL INVESTIGATOR:
Pietro Iaffaldano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

Long-Term Evaluation of Effectiveness and Immunological Implications of Ocrelizumab in a Real-World Cohort

REFERENCE

Guerra T, Caputo F, Bianco A, Paolicelli D, Iaffaldano P. *Long-Term Evaluation of Effectiveness and Immunological Implications of Ocrelizumab in a Real-World Cohort.* **Drugs Real World Outcomes. 2025** Mar 14. doi: 10.1007/s40801-025-00486-x

BACKGROUND AND OBJECTIVES

Extended follow-up data from real-world cohorts of patients with multiple sclerosis treated with ocrelizumab (OCR) are becoming widely available. This monocentric retrospective study aimed to evaluate the long-term effectiveness of OCR and its impact on immunoglobulin (Ig) levels, lymphocyte subsets, and infections in a cohort of patients with relapsing remitting, primary progressive, and secondary progressive multiple sclerosis.

METHODS

Patients followed at the Multiple Sclerosis Center of Bari with ≥ 2 years of OCR treatment were retrospectively recruited in 2024. Twelve-month confirmed disability worsening, improvement, and the annualized relapse rate before and after treatment start were estimated and follow-up magnetic resonance imaging scans were collected. Changes in IgG/IgM/IgA levels from baseline for up to 6 years of OCR treatment and serum levels of T CD4+, T CD8+, and natural killer lymphocytes were assessed. Infection occurrence, type, and outcomes were investigated. Multivariable Cox models examined the association of clinical and radiological baseline factors with the risk of confirmed disability worsening and the relationship of infections with clinical-laboratoristic risk factors.

RESULTS

The final cohort retrieved 140 patients (80 relapsing remitting, 37 primary progressive, 23 secondary progressive) with a median (interquartile range) follow-up after treatment start of 4.62 (4.10–5.04) years. In the entire cohort, the mean annualized relapse rate decreased from 0.61 in the year before the start of OCR treatment to 0.02 in the second year, thereafter all patients in our cohort remained free of relapses and magnetic resonance imaging activity. The overall percentage of stable patients increased from the second to the fourth year, in parallel with a reduction in patients with confirmed disability worsening. A multifocal onset and the presence of at least two relapses before the start of OCR treatment were significant ($p < 0.05$) risk factors of confirmed disability worsening. During the follow-up, a reduction in the IgG serum level was observed, which further decreased, becoming stable after the third year. Immunoglobulin M levels slightly decreased over time, whereas IgA levels remained stable. No changes for T CD4+, natural killer cell absolute number, and a slight reduction in T CD8+ lymphocytes during follow-up were observed. Ocrelizumab did not determine a significant infection risk in the long term and no association was observed with Ig levels and severe infections.

CONCLUSIONS

Ocrelizumab prevented disease activity over the long term and its effect on the immune system did not determine a significant infection risk in most patients.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: ANALYTICAL EPIDEMIOLOGY - PROGNOSTIC FACTORS

TITLE: **ASsessing Long Term effectiveness of OcrelizumAb in ITalian Multiple Sclerosis Registry: a cOmparisoN on PIRA and RAW in early vs delaYed treatment**

PRINCIPAL INVESTIGATOR:
Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

Registers as central real world data source: the experience of the Italian Multiple Sclerosis and Related Disorders Register

REFERENCE

Ponzio M, Battaglia MA, Trojano M, Salivetto M, D'Ettorre A, Corrado D, Paletta P, Lepore V, Mosconi P; Comitato Scientifico del Registro Italiano Sclerosi Multipla e Patologie Correlate; Rete dei centri del Registro Italiano Sclerosi Multipla e Patologie Correlate; Rete degli assistenti di ricerca del Registro Italiano Sclerosi Multipla e Patologie Correlate. *I registri come importante fonte di real world data: l'esperienza del* Registro Italiano Sclerosi Multipla e Patologie Correlate *[Registers as central real world data source: the experience of the* Italian Multiple Sclerosis and Related Disorders Register*]*. **Epidemiol Prev. 2024** Jul-Oct;48(4-5):361-374. Italian. doi: 10.19191/EP24.4-5.A734.074

Registers collecting data from clinical practice (real world data) have gained increasing interest in recent years in the scientific, administrative, and regulatory fields. The value of longitudinal data collection in deepening knowledge about a specific pathology and its healthcare complexity is increasingly recognized. This article describes the development, organizational structure, and technical characteristics of the Italian Multiple Sclerosis and Related Disorders Register (RISM). This multicentre and prospective study gathers demographic, clinical, and epidemiological data from the Italian population with multiple sclerosis and related diseases. The study, officially launched in 2015, but containing data collected since the 1990's, currently involves

the active participation of 136 specialized clinical centres and more than 80,000 enrolled patients. The analysis of data in RISM allows for a detailed description of the characteristics of multiple sclerosis and related diseases, providing new insights useful for healthcare planning, cost evaluation, treatment efficacy and safety assessment, and scientific research studies. The main demographic and clinical data of enrolled patients are reported, with a focus on specific study cohorts. In a continuous effort to improve data quality, RISM has implemented specific quality indicators. Starting from the RISM experience, crucial aspects such as the institutional recognition of the disease register, the contribution that register can provide in pharmacovigilance studies, the organizational and management challenges, and privacy issues are discussed.

Disease-modifying treatment and disability progression in subclasses of patients with primary progressive MS: results from the Big MS Data Network

REFERENCE

Lorscheider J, Signori A, Subramaniam S, Benkert P, Vukusic S, Trojano M, Hillert J, Glaser A, Hyde R, Spelman T, Magyari M, Elberling F, Pontieri L, Koch-Henriksen N, Sørensen PS, Gerlach O, Prat A, Girard M, Eichau S, Grammond P, Horakova D, Ramo-Tello C, Roos I, Buzzard K, Lechner Scott J, Sánchez-Menoyo JL, Alroughani R, Prévost J, Kuhle J, Gray O, Mathey G, Michel L, Ciron J, De Sèze J, Maillart E, Ruet A, Labauge P, Zephir H, Kwiatkowski A, van der Walt A, Kalincik T, Butzkueven H; Italian MS Register; Observatoire Français de la Sclérose en Plaques (OFSEP); MSBase Study Group; Swedish MS Registry; Big MS Data Network. *Disease-modifying treatment and disability progression in subclasses of patients with primary progressive MS: results from the Big MS Data Network.* **J Neurol Neurosurg Psychiatry. 2024** Dec 6:jnnp-2024-334700. doi: 10.1136/jnnp-2024-334700

BACKGROUND

Effectiveness of disease-modifying treatment (DMT) in people affected by primary progressive multiple sclerosis (PPMS) is limited. Whether specific subgroups may benefit more from DMT in a real-world setting remains unclear. Our aim was to investigate the potential effect of DMT on disability worsening among patients with PPMS stratified by different disability trajectories.

METHODS

Within the framework of the Big MS Data network, we merged data from the Observatoire Français de la Sclérose en Plaques, the Swedish and Italian MS registries, and MSBase. We identified patients with PPMS that started DMT or were never treated during the observed period. Subpopulations with comparable baseline characteristics were selected by propensity score matching. Disability outcomes were analysed in time-to-recurrent event analyses, which were repeated in subclasses with different disability trajectories determined by latent class mixed models.

RESULTS

Of the 3,243 included patients, we matched 739 treated and 1,330 untreated patients with a median follow-up of 3 years after pairwise censoring. No difference in the risk of confirmed disability worsening (CDW) was observed between the groups in the fully matched dataset (HR 1.11, 95% CI 0.97 to 1.23, p=0.127). However, we found a lower risk for CDW among the class of treated patients with an aggressive disability trajectory (n=360, HR 0.68, 95% CI 0.50 to 0.92, p=0.014).

CONCLUSIONS

In line with previous studies, our data suggest that DMT does not ameliorate disability worsening in PPMS, in general. However, we observed a beneficial effect of DMT on disability worsening in patients with aggressive predicted disability trajectories.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS, SAFETY

TITLE: **Big Multiple Sclerosis Data (BMSD) network**

PRINCIPAL INVESTIGATOR:
Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

Active and non-active secondary progressive multiple sclerosis patients exhibit similar disability progression: results of an Italian MS registry study (ASPERA)

REFERENCE

Chisari CG, Amato MP, Di Sapio A, Foschi M, Iaffaldano P, Inglese M, Fermo SL, Lugaresi A, Lus G, Mascoli N, Montepietra S, Pesci I, Quatrale R, Salemi G, Torri Clerici V, Totaro R, Valentino P, Filippi M, Patti F. *Active and non-active secondary progressive multiple sclerosis patients exhibit similar disability progression: results of an Italian MS registry study (ASPERA).* **J Neurol. 2024** Oct;271(10):6801-6810. doi: 10.1007/s00415-024-12621-9.

'Active' and 'non-active' secondary progressive MS (SPMS) have distinct pathophysiological mechanisms and clinical characteristics, but there is still no consensus regarding the frequency of these MS forms in the real-world setting. We aimed to evaluate the frequency of 'active' and 'non-active' SPMS in a large cohort of Italian MS patients and the differences in terms of clinical and MRI characteristics and disease progression. This multicenter study collected data about MS patients who have transitioned to the SP form in the period between 1st January 2014 and 31st December 2019 and followed by the MS centers contributing to the Italian MS Registry. Patients were divided into 'active SPMS' and 'non-active SPMS', based on both reported MRI data and relapse activity in the year before conversion to SPMS. Out of 68,621, 8,316 (12.1%) patients were diagnosed with SPMS. Out of them, 872 (10.5%) were classified into patients with either 'active' or 'non-active' SPMS. A total of 237 were classified into patients with 'active SPMS' (27.2%) and 635 as 'non-

active SPMS' (72.8%). 'Non-active SPMS' patients were older, with a longer disease duration compared to those with 'active SPMS'. The percentages of patients showing progression independent of relapse activity (PIRA) at 24 months were similar between 'active' and 'non-active' SPMS patients (67 [27.4%] vs 188 [29.6%]; p = 0.60). In the 'active' group, 36 (15.2%) patients showed relapse-associated worsening (RAW). Comparison of the survival curves to EDSS 6 and 7 according to disease activity did not show significant differences (p = 0.68 and p = 0.71). 'Active' and 'non-active' SPMS patients had a similar risk of achieving disability milestones, suggesting that progression is primarily attributed to PIRA and only to a small extent to disease activity.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: ANALYTICAL EPIDEMIOLOGY - PROGNOSTIC FACTORS

TITLE: **Evaluating the clinicAl and MRI characteristics of Secondary Progressive multiplE sclerosis; a registRy-bAsed/multicentric cohort study (ASPERA)**

PRINCIPAL INVESTIGATOR:

Francesco Patti, Dipartimento di Scienze Mediche e Chirurgiche e Tecnologie Avanzate, GF Ingrassia, Sezione Neuroscienze, Centro Sclerosi Multipla, Università degli Studi di Catania, Catania, Italia

Disability trajectories by progression independent of relapse activity status differ in pediatric, adult and late-onset multiple sclerosis

REFERENCE

Simone M, Lucisano G, Guerra T, et al. *Disability trajectories by progression independent of relapse activity status differ in pediatric, adult and late-onset multiple sclerosis.* **J Neurol. 2024** Ago 23; 271(10):6782-6790. doi:10.1007/s00415-024-12638-0

BACKGROUND

To compare Expanded Disability Status Scale (EDSS) trajectories over time between Multiple Sclerosis (MS) groups with pediatric (POMS), adult (AOMS) and late (LOMS) onset, and between patients with and without progression independent of relapse activity (PIRA).

METHODS

Patients with a first visit within 1 year from onset, ≥ 5-year follow-up and ≥ 1 visit every 6 months were selected from the Italian MS Register. Adjusted disability trajectories were assessed by longitudinal models for repeated measures. Comparisons between groups and between patients with and without PIRA in subgroups were performed by evaluating the yearly differences of mean EDSS score changes versus baseline (delta-EDSS). A first CDA event was defined as a 6-months confirmed disability increase from study baseline, measured by EDSS (increase ≥ 1.5 points with baseline EDSS = 0; ≥ 1.0 with baseline EDSS score ≤ 5.0 and ≥ 0.5 point with baseline EDSS > 5.5). PIRA was defined as a CDA

event occurring more than 90 days after and more than 30 days before the onset of a relapse.

RESULTS

3777 MS patients (268 POMS, 3282 AOMS, 227 LOMS) were included. The slope of disability trajectories significantly diverged in AOMS vs POMS starting from the second year of follow-up (Year 2: delta2-EDSS 0.18 (0.05; 0.31), $p = 0.0054$) and then mean delta2-EDSS gradually increased up to 0.23 (0.07; 0.39, $p = 0.004$) at year 5. Patients with PIRA had significant ($p < 0.0001$) steeper increase in EDSS scores than those without PIRA in all groups, although in POMS, the disability trajectories began to diverge later and at a lesser extent with delta-EDSS score of 0.48 vs 0.83 in AOMS and 1.57 in LOMS, at 3 years after the first PIRA.

CONCLUSIONS

Age is relevant in determining disability progression in MS. POMS shows a less steep increase in EDSS scores over time than older patients. The effect of PIRA in accelerating EDSS progression is less pronounced in POMS than in AOMS and LOMS.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - COMPARATIVE EFFECTIVENESS / SAFETY BETWEEN TREATMENTS

TITLE: **Multi-centre, prospective/retrospective, randomised, open label pragmatic trial to compare the effectiveness and safety of interferon beta-1a (IFN beta-1a)**

PRINCIPAL INVESTIGATOR:

Marta Simone, Unità di Neuropsichiatria Infantile, Dipartimento di Medicina di Precisione e Rigenerativa e Area Jonica (DiMePRe-J), Università di Bari, Bari, Italia

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

REFERENCE

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

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - COMPARATIVE EFFECTIVENESS / SAFETY BETWEEN TREATMENTS

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

PRINCIPAL INVESTIGATOR:

Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

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

REFERENCE

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

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: DESCRIPTIVE EPIDEMIOLOGY

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

PRINCIPAL INVESTIGATOR:

Roberto Bergamaschi, U.O. Sclerosi Multipla IRCCS Fondazione Istituto Neurologico Nazionale "C. Mondino", Pavia, Italia; on behalf Comitato Scientifico del Registro Italiano SM e Patologie Correlate

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

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS, SAFETY

TITLE: **Big Multiple Sclerosis Data (BMSD) Network**

PRINCIPAL INVESTIGATOR:
Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

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

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS, SAFETY

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

PRINCIPAL INVESTIGATOR:

Francesco Patti, Dipartimento di Scienze Mediche e Chirurgiche e Tecnologie Avanzate, GF Ingrassia, Sezione Neuroscienze, Centro Sclerosi Multipla, Università degli Studi di Catania, Catania, Italia. On behalf of the Italian MS Register Study Group

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

REFERENCE

Portaccio E, Betti M, De Meo E, Addazio I, Pastò L, Razzolini L, Totaro R, Spitaleri D, Lugaresi A, Cocco E, Onofrj M, Di Palma F, Patti F, Maimone D, Valentino P, Torri Clerici V, Protti A, Ferraro D, Lus G, Maniscalco GT, Brescia Morra V, Salemi G, Granella F, Pesci I, Bergamaschi R, Aguglia U, Vianello M, Simone M, Lepore V, Iaffaldano P, Comi G, Filippi M, Trojano M, Amato MP Italian Multiple Sclerosis Register. *Progression independent of relapse activity in relapsing multiple sclerosis: impact and relationship with secondary progression* **J Neurol. 2024** May 28. doi: 10.1007/s00415-024-12448-4

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 8,998 (55.8%) patients. PIRA (12,175) accounted for 72.3% of CDA. SDA occurred in 8,912 (73.2%) PIRA and 2,583 (56.7%) RAW ($p < 0.001$). 4453 (27.6%) patients transitioned to SPMS, 4,010 (73.2%) out of 5,476 patients with sustained PIRA and 443 (24.8%) out of 1,790 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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - COMPARATIVE EFFECTIVENESS/ SAFETY BETWEEN TREATMENTS

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

PRINCIPAL INVESTIGATOR:

Emilio Portaccio, Dipartimento NEUROFARBA, Divisione di Riabilitazione Neurologica, Azienda Ospedaliero- Universitaria Careggi; IRCCS Fondazione Don Carlo Gnocchi, Firenze, Italia

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

REFERENCE

Sharmin S, Roos I, Malpas CB, Iaffaldano P, Simone M, Filippi M, Kubala Havrdova E, Ozakbas S, Brescia Morra V, Alroughani R, Zaffaroni M, Patti F, Eichau S, Salemi G, Di Sapio A, Inglese M, Portaccio E, Trojano M, Amato MP, Kalincik T; Writing Group; Italian Multiple Sclerosis and Related Disorders Register and MSBase Study Group. *Disease-modifying therapies in managing disability worsening in paediatric-onset multiple sclerosis: a longitudinal analysis of global and national registries.* **Lancet Child Adolesc Health. 2024** May;8(5):348-357. doi: 10.1016/S2352-4642(24)00047-6

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 5,224 people (3,686 [70·6%] female and 1,538 [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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - COMPARATIVE EFFECTIVENESS/ SAFETY BETWEEN TREATMENTS

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

PRINCIPAL INVESTIGATOR:

Tomas Kalincik, Clinical Outcomes Research Unit, Department of Medicine, University of Melbourne, Melbourne, VIC, Australia

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

REFERENCE

Lorefice L, Ferraro OE, Fenu G, Amato MP, Bresciamorra V, Conte A, De Luca G, Ferraro D, Filippi M, Gazzola P, Iaffaldano P, Inglese M, Lus G, Marfia GA, Patti F, Pesci I, Salemi G, Trojano M, Zaffaroni M, Monti MC, Cocco E; Italian MS Register. *Late-onset multiple sclerosis: disability trajectories in relapsing-remitting patients of the Italian MS Registry.* **J Neurol. 2024 Apr;** 271(4):1630-1637. doi: 10.1007/s00415-023-12152 9

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 [1,012 (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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: DESCRIPTIVE EPIDEMIOLOGY

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

PRINCIPAL INVESTIGATOR:

Lorena Lorefice, Centro Regionale per la Diagnosi e Cura della Sclerosi Multipla, Università degli Studi di Cagliari, ASL Cagliari, Italia

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

REFERENCE

Iaffaldano P, Lucisano G, Guerra T, Patti F, Cocco E, De Luca G, Brescia Morra V, Pozzilli C, Zaffaroni M, Ferraro D, Gasperini C, Salemi G, Bergamaschi R, Lus G, Inglese M, Romano S, Bellantonio P, Di Monte E, Maniscalco GT, Conte A, Lugaresi A, Vianello M, Torri Clerici VLA, Di Sapio A, Pesci I, Granella F, Totaro R, Marfia GA, Danni MC, Cavalla P, Valentino P, Aguglia U, Montepietra S, Ferraro E, Protti A, Spitaleri D, Avolio C, De Riz M, Maimone D, Cavaletti G, Gazzola P, Tedeschi G, Sessa M, Rovaris M, Di Palma F, Gatto M, Cargnelutti D, De Robertis F, Logullo FO, Rini A, Meucci G, Ardito B, Banfi P, Nasuelli D, Paolicelli D, Rocca MA, Portaccio E, Chisari CG, Fenu G, Onofrj M, Carotenuto A, Ruggieri S, Tortorella C, Ragonese P, Nica M, Amato MP, Filippi M, Trojano M; Italian MS Register. *Evaluation of drivers of treatment switch in relapsing multiple sclerosis: a study from the Italian MS Registry.* **J Neurol. 2024** Mar;271(3):1150-1159. doi: 10.1007/s00415-023-12137-8

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 4,739 RMS patients (4,161 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

PRIORITY AREA: THERAPY – TREATMENT ALGORITHMS AND SWITCHES

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

PRINCIPAL INVESTIGATOR:

Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

Predictors of treatment switching in the Big Multiple Sclerosis Data Network

REFERENCE

Spelman T, Magyari M, Butzkueven H, Van Der Walt A, Vukusic S, Trojano M, Iaffaldano P, Horáková D, Drahota J, Pellegrini F, Hyde R, Duquette P, Lechner-Scott J, Sajedi SA, Lalive P, Shaygannejad V, Ozakbas S, Eichau S, Alroughani R, Terzi M, Girard M, Kalincik T, Grand'Maison F, Skibina O, Khoury SJ, Yamout B, Sa MJ, Gerlach O, Blanco Y, Karabudak R, Oreja-Guevara C, Altintas A, Hughes S, McCombe P, Ampapa R, de Gans K, McGuigan C, Soysal A, Prevost J, John N, Inshasi J, Stawiarz L, Manouchehrinia A, Forsberg L, Sellebjerg F, Glaser A, Pontieri L, Joensen H, Rasmussen PV, Sejbaek T, Poulsen MB, Christensen JR, Kant M, Stilund M, Mathiesen H, Hillert J; Big MS Data Network: a collaboration of the Czech MS Registry, the Danish MS Registry, Italian MS Registry, Swedish MS Registry, MSBase Study Group, and OFSEP. *Predictors of treatment switching in the Big Multiple Sclerosis Data Network*. **Front Neurol. 2023** Dec;14:1274194. doi: 10.3389/fneur.2023.1274194

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 started 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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS, SAFETY

TITLE: **Big Multiple Sclerosis Data (BMSD) Network**

PRINCIPAL INVESTIGATOR:

Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

Multiple Sclerosis Progression and Relapse Activity in Children

REFERENCE

Iaffaldano P, Portaccio E, Lucisano G, Simone M, Manni A, Guerra T, Paolicelli D, Betti M, De Meo E, Pastò L, Razzolini L, Rocca MA, Ferrè L, Brescia Morra V, Patti F, Zaffaroni M, Gasperini C, De Luca G, Ferraro D, Granella F, Pozzilli C, Romano S, Gallo P, Bergamaschi R, Coniglio MG, Lus G, Vianello M, Banfi P, Lugaresi A, Totaro R, Spitaleri D, Cocco E, Di Palma F, Maimone D, Valentino P, Torri Clerici V, Protti A, Maniscalco GT, Salemi G, Pesci I, Aguglia U, Lepore V, Filippi M, Trojano M, Amato MP; Italian Multiple Sclerosis Register. *Multiple Sclerosis Progression and Relapse Activity in Children.* **JAMA Neurol. 2024** Jan;81(1):50-58. doi: 10.1001/jamaneurol.2023.4455

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

This 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 7,176 patients (44.5%): 558 patients with POMS (40.4%), 6,258

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

PRIORITY AREA: THERAPY - PROGNOSTIC FACTORS AND PREDICTIVE MODELS OF TREATMENT RESPONSE

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

PRINCIPAL INVESTIGATOR:
Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

COVID19 outbreak in Italy: an opportunity to evaluate extended interval dosing of ocrelizumab in MS patients

REFERENCE

Bisecco A, Matrone F, Capobianco M, De Luca G, Filippi M, Granella F, Lus G, Marfia GA, Mirabella M, Patti F, Trojano M, Mascolo A, Copetti M, Tedeschi G, Gallo A; OCREVID study group on behalf of the Italian MS Register. *COVID-19 outbreak in Italy: an opportunity to evaluate extended interval dosing of ocrelizumab in MS patients.* **J Neurol. 2024** Feb;271(2):699-710. doi: 10.1007/s00415-023-12084-4

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY – TREATMENT ADHERENCE

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

PRINCIPAL INVESTIGATOR:

Antonio Gallo, Centro SM e Unità di Ricerca 3T-MRI, Dipartimento di Scienze Mediche e Chirurgiche Avanzate (DAMSS), Università della Campania "Luigi Vanvitelli", Napoli, Italia

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

REFERENCE

Chisari CG, Bianco A, Brescia Morra V, Calabrese M, Capone F, Cavalla P, Chiavazza C, Comi C, Danni M, Filippi M, Iaffaldano P, Lanzillo R, Lo Fermo S, Lucisano A, Lugaresi A, Lus G, Marfia GA, Marinelli F, Mirabella M, Moiola L, Perin C, Realmuto S, Toscano S, Trojano M, Vecchio D, Patti F; Italian MS Registry. *Effectiveness of Ocrelizumab in Primary Progressive Multiple Sclerosis: a Multicenter, Retrospective, Real-world Study (OPPORTUNITY).* **Neurotherapeutics. 2023** Oct;20(6):1696-1706. doi: 10.1007/s13311-023 01415-y

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

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

PRINCIPAL INVESTIGATOR:

Francesco Patti, Dipartimento di Scienze Mediche e Chirurgiche e Tecnologie Avanzate, GF Ingrassia, Sezione Neuroscienze, Centro Sclerosi Multipla, Università degli Studi di Catania, Catania, Italia

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

REFERENCE

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** Nov;44(11):4001-4011. doi: 10.1007/s10072-023-06876-9

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

REFERENCE

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

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

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

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

PRINCIPAL INVESTIGATOR:

Emanuele D'Amico, Dipartimento Di Scienze Mediche, Chirurgiche e Tecnologie Avanzate, Università degli Studi di Catania, Catania, Italia

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

REFERENCE

Boffa G, Signori A, Massacesi L, Mariottini A, Sbragia E, Cottone S, Amato MP, Gasperini C, Moiola L, Meletti S, Repice AM, Brescia Morra V, Salemi G, Patti F, Filippi M, De Luca G, Lus G, Zaffaroni M, Sola P, Conte A, Nistri R, Aguglia U, Granella F, Galgani S, Caniatti LM, Lugaresi A, Romano S, Iaffaldano P, Cocco E, Saccardi R, Angelucci E, Trojano M, Mancardi GL, Sormani MP, Inglese M; Italian BMT-MS Study Group and *the* Italian MS Register. *Hematopoietic Stem Cell Transplantation in People With Active Secondary Progressive MultipleSclerosis.* **Neurology. 2023** Mar;100(11):e1109-e1122. doi: 10.1212/WNL.0000000000206750

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 1,975 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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

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

PRINCIPAL INVESTIGATOR:

Matilde Inglese, Dipartimento di Neuroscienze, Riabilitazione Oftalmologia, Genetica e Scienze Materno-Infantili (DINOGMI) Università degli Studi di Genova, Genova, Italia. On behalf of the Italian BMT-MS Study Group and the Italian MS Register

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

REFERENCE

Signori A, Lorscheider J, Vukusic S, Trojano M, Iaffaldano P, Hillert J, Hyde R, Pellegrini F, Magyari M, Koch-Henriksen N, Sørensen PS, Spelman T, van der Walt A, Horakova D, Havrdova E, Girard M, Eichau S, Grand'Maison F, Gerlach O, Terzi M, Ozakbas S, Skibina O, Van Pesch V, Sa MJ, Prevost J, Alroughani R, McCombe PA, Gouider R, Mrabet S, Castillo-Trivino T, Zhu C, de Gans K, Sánchez-Menoyo JL, Yamout B, Khoury S, Sormani MP, Kalincik T, Butzkueven H; Big MS Data Network. Big MS Data Network. *Heterogeneity on long-term disability trajectories in patients with secondary progressive MS: a latent class analysis from Big MS Data network.* **J Neurol Neurosurg Psychiatry. 2022 Sep**: jnnp-2022-329987. doi: 10.1136/jnnp-2022-329987

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 3,613 patients with SPMS were included in the cohort 1. LCGA detected three different subgroups of patients with a mild (n=1,297; 35.9%), a moderate (n=1,936; 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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS, SAFETY

TITLE: **Big Multiple Sclerosis Data (BMSD) Network**

PRINCIPAL INVESTIGATOR:
Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università degli Studi di Bari, Bari, Italia

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

REFERENCE

Iaffaldano P, Lucisano G, Guerra T, Patti F, Onofrj M, Brescia Morra V, Zaffaroni M, Pozzilli C, Cocco E, Sola P, Salemi G, Inglese M, Bergamaschi R, Gasperini C, Conte A, Salvetti M, Lus G, Maniscalco GT, Totaro R, Vianello M, Granella F, Ferraro E, Aguglia U, Gatto M, Sangalli F, Chisari CG, De Luca G, Carotenuto A, Baroncini D, Colombo D, Nica M, Paolicelli D, Comi G, Filippi M, Amato MP, Trojano M. *Towards a validated definition of the clinical transition to secondary progressive multiple sclerosis: A study from the* Italian MS Register. **Mult Scler. 2022** Dec;28(14):2243-2252. doi: 10.1177/13524585221114007

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, 1,806 (17.6%) applying the DDA and 1,134 (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

PRIORITY AREA: DESCRIPTIVE EPIDEMIOLOGY

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

PRINCIPAL INVESTIGATOR:

Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università degli Studi di Bari, Bari, Italia

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

REFERENCE

Portaccio E, Fonderico M, Iaffaldano P, Pastò L, Razzolini L, Bellinvia A, De Luca G, Ragonese P, Patti F, Brescia Morra V, Cocco E, Sola P, Inglese M, Lus G, Pozzilli C, Maimone D, Lugaresi A, Gazzola P, Comi G, Pesci I, Spitaleri D, Rezzonico M, Vianello M, Avolio C, Logullo FO, Granella F, Salvetti M, Zaffaroni M, Lucisano G, Filippi M, Trojano M, Amato MP; Italian Multiple Sclerosis Register Centers Group. *Disease-Modifying Treatments and Time to Loss of Ambulatory Function in Patients With Primary Progressive Multiple Sclerosis.* **JAMA Neurol. 2022** Sep;79(9):869-878. doi: 10.1001/jamaneurol.2022.1929.

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 3,298 patients with PPMS, 2,633 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

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

TITLE: **Assessing Efficacy and Safety of treatments in progressive Multiple Sclerosis**

PRINCIPAL INVESTIGATOR:

Maria Pia Amato, Dipartimento NEUROFARBA, Divisione di Riabilitazione Neurologica, Azienda Ospedaliero- Universitaria Careggi; IRCCS Fondazione Don Carlo Gnocchi, Firenze, Italia

Do patients' and referral centers' characteristics influence multiple sclerosis phenotypes? Results from the Italian multiple sclerosis and related disorders register

REFERENCE

Bergamaschi R, Beghi E, Bosetti C, Ponzio M, Santucci C, Lepore V, Mosconi P; Italian Multiple Sclerosis and Related Disorders Register Centers Group and the Scientific Committee of Italian SM and Related Disorders Register; Aguglia U, Amato MP, Ancona AL, Ardito B, Avolio C, Balgera R, Banfi P, Barcella V, Barone P, Bellantonio P, Berardinelli A, Bergamaschi R, Bertora P, Bianchi M, Bramanti P, Morra VB, Brichetto G, Brioschi AM, Buccafusca M, Bucello S, Busillo V, Calchetti B, Cantello R, Capobianco M, Capone F, Capone L, Cargnelutti D, Carrozzi M, Cartechini E, Cavaletti G, Cavalla P, Celani MG, Clerici R, Clerico M, Cocco E, Confalonieri P, Coniglio MG, Conte A, Corea F, Cottone S, Crociani P, D'Andrea F, Danni MC, De Luca G, de Pascalis D, De Riz M, De Robertis F, De Rosa G, De Stefano N, Corte MD, Di Sapio A, Docimo R, Falcini M, Falcone N, Fermi S, Ferraro E, Ferrò MT, Fortunato M, Foschi M, Gajofatto A, Gallo A, Gallo P, Gatto M, Gazzola P, Giordano A, Granella F, Grasso MF, Grasso MG, Grimaldi LME, Iaffaldano P, Imperiale D, Inglese M, Iodice R, Leva S, Luezzi V, Lugaresi A, Lus G, Maimone D, Mancinelli L, Maniscalco GT, Marfia GA, Marini B, Marson A, Mascoli N, Massacesi L, Melani F, Merello M, Meucci G, Mirabella M,

Montepietra S, Nasuelli D, Nicolao P, Passantino F, Patti F, Peresson M, Pesci I, Piantadosi C, Piras ML, Pizzorno M, Plewnia K, Pozzilli C, Protti A, Quatrale R, Realmuto S, Ribizzi G, Rinalduzzi S, Rini A, Romano S, Romeo M, Ronzoni M, Rossi P, Rovaris M, Salemi G, Santangelo G, Santangelo M, Santuccio G, Sarchielli P, Sinisi L, Sola P, Solaro C, Spitaleri D, Strumia S, Tassinari T, Tonietti S, Tortorella C, Totaro R, Tozzo A, Trivelli G, Ulivelli M, Valentino P, Venturi S, Vianello M, Zaffaroni M, Zarbo R, Trojano M, Battaglia MA, Capobianco M, Pugliatti M, Ulivelli M, Mosconi P, Gasperini C, Patti F, Amato MP, Bergamaschi R, Comi G. *Do patients' and referral centers' characteristics influence multiple sclerosis phenotypes? Results from the* ***Italian multiple sclerosis and related disorders register***. **Neurol Sci. 2022** Sep; 43(9):5459-5469. doi: 10.1007/s10072-022-06169-7

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: DESCRIPTIVE EPIDEMIOLOGY

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

PRINCIPAL INVESTIGATOR:

Roberto Bergamaschi, U.O. Sclerosi Multipla IRCCS Fondazione Istituto Neurologico Nazionale "C. Mondino", Pavia, Italia; on behalf Comitato Scientifico del Registro Italiano SM e Patologie Correlate

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

REFERENCE

Portaccio E, Bellinvia A, Fonderico M, Pastò L, Razzolini L, Totaro R, Spitaleri D, Lugaresi A, Cocco E, Onofrj M, Di Palma F, Patti F, Maimone D, Valentino P, Confalonieri P, Protti A, Sola P, Lus G, Maniscalco GT, Brescia Morra V, Salemi G, Granella F, Pesci I, Bergamaschi R, Aguglia U, Vianello M, Simone M, Lepore V, Iaffaldano P, Filippi M, Trojano M, Amato MP; Italian Multiple Sclerosis Register. *Progression is independent of relapse activity in early multiple sclerosis: a real-life cohort study.* **Brain. 2022** Aug;145(8):2796-2805. doi: 10.1093/brain/awac111

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 1,427 (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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: MS AND RD COURSES

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

PRINCIPAL INVESTIGATOR:

Maria Pia Amato, Dipartimento di NEUROFARBA, Università di Firenze, IRCCS Fondazione Don Carlo Gnocchi, Firenze, Italia

Comparing Natural History of Early and Late Onset Pediatric Multiple Sclerosis

REFERENCE

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

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - PROGNOSTIC FACTORS AND PREDICTIVE MODELS OF TREATMENT RESPONSE

TITLE: **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

REFERENCE

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

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

PRIORITY AREA: THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

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

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

REFERENCE

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

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) study 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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: ANALYTICAL EPIDEMIOLOGY

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

PRINCIPAL INVESTIGATOR:

Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

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

REFERENCE

Zanghì A, Avolio C, Amato MP, Filippi M, Trojano M, Patti F, D'Amico E; Italian MS register. First-line therapies in late-onset multiple sclerosis: An Italian registry study. **Eur J Neurol. 2021** Dec;28(12):4117-4123. doi: 10.1111/ene.15006

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 3,989 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

PRIORITY AREA: PRIORITY THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

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

PRINCIPAL INVESTIGATOR:

Emanuele D'Amico, Dipartimento Di Scienze Mediche, Chirurgiche e Tecnologie Avanzate, Università degli Studi di Catania, Catania, Italia

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

REFERENCE

Ferraro D, Iaffaldano P, Guerra T, Inglese M, Capobianco M, Brescia Morra V, Zaffaroni M, Mirabella M, Lus G, Patti F, Cavalla P, Cellerino M, Malucchi S, Pisano E, Vitetta F, Paolicelli D, Sola P, Trojano M; Italian MS Register. *Risk of multiple sclerosis relapses when switching from fingolimod to cell-depleting agents: the role of washout duration.* **J Neurol. 2022** Mar;269(3):1463-1469. doi: 10.1007/s00415-021-10708-1

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

PRIORITY AREA: THERAPY - PROGNOSTIC FACTORS AND PREDICTIVE MODELS OF TREATMENT RESPONSE

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

PRINCIPAL INVESTIGATOR:

Diana Ferraro, Centro Malattie Demielinizzanti - Clinica Neurologica dell'Università di Modena e Reggio Emilia, Ospedale Civile S. Agostino Estense, Modena, Italia

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

REFERENCE

Chisari CG, Comi G, Filippi M, Paolicelli D, Iaffaldano P, Zaffaroni M, Brescia Morra V, Cocco E, Marfia GA, Grimaldi LM, Inglese M, Bonavita S, Lugaresi A, Salemi G, De Luca G, Cottone S, Conte A, Sola P, Aguglia U, Maniscalco GT, Gasperini C, Ferrò MT, Pesci I, Amato MP, Rovaris M, Solaro C, Lus G, Maimone D, Bergamaschi R, Granella F, Di Sapio A, Bertolotto A, Totaro R, Vianello M, Cavalla P, Bellantonio P, Lepore V, Patti F; Italian MS Register Study Group. *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*. **J Neurol. 2022** Feb;269(2):933-944. doi: 10.1007/s00415-021-10676-6

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, 5,151 patients, 3019 (58.6%) females, with a mean age of 43.6±10.1 years (median 40), were analyzed. Out of 2,037 (39.5%) who discontinued NTZ, a significantly higher percentage suspended NTZ because of PML risk compared to lack of efficacy [1,682 (32.7% of 5,151) 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).

CONCLUSIONS

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

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

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

PRINCIPAL INVESTIGATOR:
Francesco Patti, Dipartimento di Scienze Mediche e Chirurgiche e Tecnologie Avanzate, GF Ingrassia, Sezione Neuroscienze, Centro Sclerosi Multipla, Università degli Studi di Catania, Catania, Italia. On behalf of the Italian MS Register Study Group

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

REFERENCE

Baroncini D, Simone M, Iaffaldano P, Brescia Morra V, Lanzillo R, Filippi M, Romeo M, Patti F, Chisari CG, Cocco E, Fenu G, Salemi G, Ragonese P, Inglese M, Cellerino M, Margari L, Comi G, Zaffaroni M, Ghezzi A; Italian MS registry. *Risk of Persistent Disability in Patients With Pediatric-Onset Multiple Sclerosis.* **JAMA Neurol. 2021 Jun**;78(6):726-735. doi: 10.1001/jamaneurol.2021.1008

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 4,704 patients with POMS. According to these criteria, we enrolled 3,198 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 3,198 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

PRIORITY AREA: MS AND RD COURSES

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

PRINCIPAL INVESTIGATOR:

Damiano Baroncini, Centro SM di Gallarate, ASST della Valle Olona, Gallarate (VA), Italia

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

REFERENCE

Iaffaldano P, Lucisano G, Caputo F, Paolicelli D, Patti F, Zaffaroni M, Brescia Morra V, Pozzilli C, De Luca G, Inglese M, Salemi G, Maniscalco GT, Cocco E, Sola P, Lus G, Conte A, Amato MP, Granella F, Gasperini C, Bellantonio P, Totaro R, Rovaris M, Salvetti M, Torri Clerici VLA, Bergamaschi R, Maimone D, Scarpini E, Capobianco M, Comi G, Filippi M, Trojano M; Italian MS Register. *Long-term disability trajectories in relapsing multiple sclerosis patients treated with early intensive or escalation treatment strategies.* **Ther Adv Neurol Disord. 2021** May;14:17562864211019574. doi: 10.1177/17562864211019574

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

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

PRINCIPAL INVESTIGATOR:

Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

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

REFERENCE

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

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

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS, SAFETY

TITLE: **Big Multiple Sclerosis Data (BMSD) Network**

PRINCIPAL INVESTIGATOR:

Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

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

REFERENCE

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

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

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

PRINCIPAL INVESTIGATOR:

Emanuele D'Amico, Dipartimento Di Scienze Mediche, Chirurgiche e Tecnologie Avanzate, Università degli Studi di Catania, Catania, Italia

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

REFERENCE

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

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

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS, SAFETY

TITLE: **Big Multiple Sclerosis Data (BMSD) Network**

PRINCIPAL INVESTIGATOR:
Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

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

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - PROGNOSTIC FACTORS AND PREDICTIVE MODELS OF TREATMENT RESPONSE

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

PRINCIPAL INVESTIGATOR:
Maria Trojano, Centro SM, Dipartimento di Scienze Mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, Italia

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

REFERENCE

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

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

PRIORITY AREA: DESCRIPTIVE EPIDEMIOLOGY

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

PRINCIPAL INVESTIGATOR:
Paola Mosconi, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italia

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

REFERENCE

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

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 5,231 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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

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

PRINCIPAL INVESTIGATOR:
Francesco Patti, Dipartimento di Scienze Mediche e Chirurgiche e Tecnologie Avanzate, GF Ingrassia, Sezione Neuroscienze, Centro Sclerosi Multipla, Università degli Studi di Catania, Catania, Italia. On behalf of the Italian MS Register Study Group

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

REFERENCE

Amato MP, Fonderico M, Portaccio E, Pastò L, Razzolini L, Prestipino E, Bellinvia A, Tudisco L, Fratangelo R, Comi G, Patti F, De Luca G, Brescia Morra V, Cocco E, Pozzilli C, Sola P, Bergamaschi R, Salemi G, Inglese M, Millefiorini E, Galgani S, Zaffaroni M, Ghezzi A, Salvetti M, Lus G, Florio C, Totaro R, Granella F, Vianello M, Gatto M, Di Battista G, Aguglia U, Logullo FO, Simone M, Lucisano G, Iaffaldano P, Trojano M. *Disease-modifying drugs can reduce disability progression in relapsing multiple sclerosis.* **Brain. 2020** Oct 1;143(10):3013-3024. doi: 10.1093/brain/awaa251

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: MS AND RD COURSES

TITLE: **E-MUSIC: Early MUltiple Sclerosis Italian Cohort**

PRINCIPAL INVESTIGATOR:

Maria Pia Amato, Dipartimento NEUROFARBA, Divisione di Riabilitazione Neurologica, Azienda Ospedaliero- Universitaria Careggi; IRCCS Fondazione Don Carlo Gnocchi, Firenze, Italia, on behalf of the Italian Multiple Sclerosis Register Centers Group

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

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

PRIORITY AREA: THERAPY - SHORT AND LONG-TERM TREATMENT EFFECTIVENESS

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

PRINCIPAL INVESTIGATOR:

Francesco Patti, Centro Sclerosi Multipla, Azienda Ospedaliera-Universitaria, Policlinico Vittorio Emanuele, Università degli Studi di Catania, Catania, Italia

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

REFERENCE

Paolicelli D, Lucisano G, Manni A, Avolio C, Bonavita S, Brescia Morra V, Capobianco M, Cocco E, Conte A, De Luca G, De Robertis F, Gasperini C, Gatto M, Gazzola P, Lus G, Iaffaldano A, Iaffaldano P, Maimone D, Mallucci G, Maniscalco GT, Marfia GA, Patti F, Pesci I, Pozzilli C, Rovaris M, Salemi G, Salvetti M, Spitaleri D, Totaro R, Zaffaroni M, Comi G, Amato MP, Trojano M; Italian MS Register. *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.*** **J Neurol. 2019** Dec;266(12):3098-3107. doi: 10.1007/s00415-019-09531-6

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.

CORRESPONDING RESEARCH PROJECT BASED ON RISM DATA

PRIORITY AREA: THERAPY - COMPARATIVE EFFECTIVENESS/SAFETY BETWEEN TREATMENTS

TITLE: **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**

PRINCIPAL INVESTIGATOR:

Damiano Paolicelli, Centro Sclerosi Multipla, Dipartimento di Scienze Mediche di Base, Neuroscienze e Organi di Senso, Università degli Studi di Bari, Policlinico di Bari, Bari, Italia

The Italian multiple sclerosis register

REFERENCE

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

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

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

REFERENCE

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

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

REFERENCE

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

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

REFERENCE

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

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

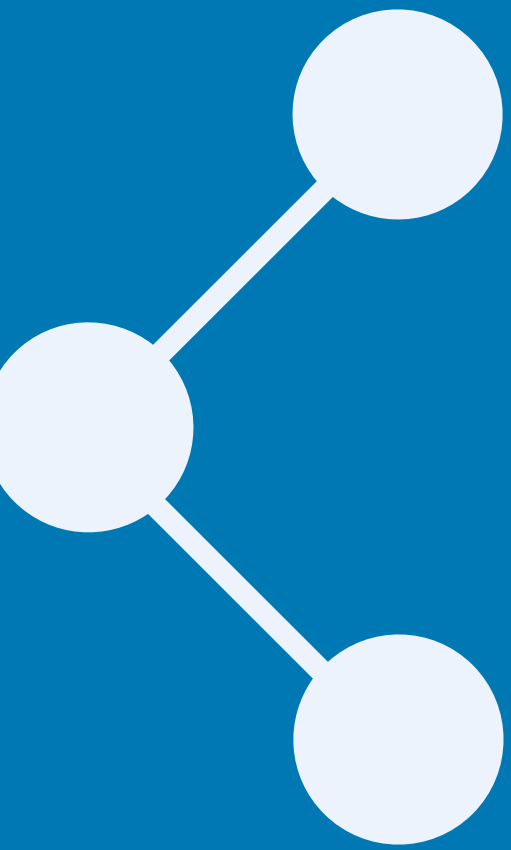
A cohort of 2570 IFNbeta-treated RRMS was prospectively followed for up to 7 years in 15 Italian MS Centers. Cox proportional hazards regression models were used to assess gender differences for risk of reaching 1st relapse and risk of progression by 1 point on Expanded Disability Status Scale (EDSS) 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.



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