ITALIAN MS REGISTER

RESEARCH PROJECTS

Technical Methodological Structure

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI - IRCCS

Network of the Italian MS Clinical Centers

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

SCLEROSI MULTIPLA ONLUS fondazione italiana

un mondo libero dalla SM

AISM. INSIEME, UNA CONQUISTA DOPO L'ALTRA

www.registroitalianosm.it

Publication date: August, 2019

Italian Multiple Sclerosis Register

The Italian Multiple Sclerosis Registry is one of the main Research Special Projects supported by AISM and its Foundation, which was launched with the aim of creating a multicentric organized infrastructure to collect the data of all patients with multiple sclerosis followed in the various multiple sclerosis (MS) centers in Italy. In 2015 a specific Research Unit was launched for the Italian SM Registry, established on the basis of a Program Agreement signed between the Italian MS Foundation (FISM) and the University of Bari (coordinating center of the largest Italian MS clinical database) in 2014. Over 140 Italian Clinical Centers have joined the project and to date, the Italian SM Registry collects demographic and clinical data of over 50,000 people followed by Italian clinical centers.
Data from the Italian Multiple Sclerosis Registry will be useful to promote the equity of access to care by comparing the welfare practices of the different Centers and to study / evaluate national and local welfare policies.

The Scientific Committee of the Italian Register SM Project has identified two strategic research priorities:

1) PROJECTS IN PUBLIC HEALTH

Need to set up a universal census of patients that is systematic and continuous update, in order to obtain accurate estimates of prevalence and incidence of the disease at regional and national level for the pursuit of prevention, diagnosis, treatment, health planning, verification of the quality of care and assessment of health care in Italy.

2) RESEARCH PROJECTS

Need to gather useful information for the planning of research studies for specific projects. In particular, pharmacovigilance studies aimed at identifying the safety, tolerability and efficacy associated, in the short and long term, with immunosuppressive and immunomodulatory treatments, as well as studies on prognostic factors and biomarkers related to disease progression, response to treatment and mortality.

The strategic research projects priorities include 3 main areas of study.

DESCRIPTIVE EPIDEMIOLOGY

Studies the frequency, the distribution and the determinants of MS in populations.

THERAPY OPTIMIZATION

Study and analysis of MS therapies. Includes three areas of work:

- Analysis of therapies
- Specific projects
- Prognostic factors and predictive models of therapy response

RARE FORMS OF MS

Focus on the different MS forms: benign forms, RIS, CIS, PP, pediatric MS onset, aggressive forms.

Currently 21 Projects have been active on the three main areas of the strategic research line:
6 descriptive epidemiology projects, 13 projects on the optimization of the therapy and 2 project on rare forms of the disease.

DESCRIPTIVE EPIDEMIOLOGY

Lorena Lorefice
Centro Regionale per la Diagnosi e la Cura della SM, Ospedale R. Binaghi, ATS Sardegna, Università degli Studi di Cagliari, Cagliari

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

Late onset of MS (LOMS), classically defined by the occurrence of the first symptoms after age 50, it is relatively infrequent and it occurs in less than 10% of patients. To date, few studies compared this population with young-adult onset MS (YOMS) patients in term of demographic and clinical characteristics, some of which assessed that LOMS more frequently features a primary progressive course, predicting a severe disability,while a recent study showed that older age at MS onset is an independent factor of poor prognosis. However, there is still uncertain information about the clinical outcomes of LOMS, the response to disease modifying treatments (DMDs) and consequently the implication for disease prognosis. The present project is a multicenter retrospective study aimed to describe the early and late clinical characteristics of LOMS in a large cohort of Italian MS patients, using YOMS as a comparator. Data of the Italian IMedWeb MS Registry will be used to perform this retrospective analysis. Firstly, patients diagnosed with MS with an age at onset of > 50 years (LOMS) will be evaluated for study and following a comparison group of YOMS cases, comprising patients with an age at MS onset between 20-40 years, will be included. LOMS and YOMS cases will be matched for sex and for disease duration. Information on age at MS onset, age at MS diagnosis, initial MS presentation, disease course (classified into either a primary progressive or relapsing course from onset), disease duration, level of disability (EDSS score) at onset and at least examination, number and type of relapses, and the use of disease modifying drugs (DMDs) will be evaluated. In addition, a progression index (EDSS score/disease duration) for each patient will be also defined. Initially, a descriptive analysis will be conducted, according to data distribution, and the demographic and clinical characteristics of the LOMS and YOMS groups were compared.

A Kaplan-Meier survival analysis will be used to estimate the time from onset to EDSS 3 and EDSS 6 within and between the LOMS and YOMS groups, and the potential risk factors associated with progression will be assessed simultaneously as covariates in a multivariate Cox regression models. The primary objective of this study is the better clinical characterization of LOMS patients in order to clarify in a large sample if late-onset is associated with a worse outcome or if the most important determinant for disease prognosis is the disease course. Furthermore, it aims to increase knowledge about the LOMS clinical phenotype and the impact that the use of DMDs may have on the number of relapses and accumulation of disability, giving new information on prognostic factors of these patients, in order to optimize their care.

DESCRIPTIVE EPIDEMIOLOGY

Giuseppe Fenu
Centro SM, Università degli Studi di Cagliari, Ospedale Binaghi, Cagliari

Changes of clinical and demographic characteristics in patients with MS diagnosis during the various decades between 1983 and 2016

It is a common observation emerging from daily clinical practice and from analysis of multiple sclerosis (MS) populations included in clinical studies that the clinical and demographic characteristics of people with multiple sclerosis have had a substantial change over the last decades. At the basis of this change, there are probably several components: evolution of diagnostic criteria, greater knowledge and attention to pathology, greater availability and technical progress of diagnostic completion tools primarily for MRI scan. In addition, the availability of effective therapies and the demonstration of the importance of early treatment, it lead to arrive at diagnosis at an increasingly early stage of the history of the disease. However, there are currently few studies that compared the clinical and demographic characteristics of patients who have been diagnosed with MS over the decades. A recent study observed in a cohort of patients a significant change in long-term prognosis in patients with post-2000 diagnosis compared to those with previous diagnosis, primarily attributing it to changes in treatment patterns. The aim of our study is to evaluate whether differences in the main clinical and demographic parameters are present in patients who have been diagnosed with MS over the decades.

For each patient, the following parameters will be evaluated: gender, age at onset, age at diagnosis, diagnostic latency (time interval between clinical onset and diagnosis), annualized relapse rate in the first 2 years of disease, time from onset to first relapse, time from onset to reach EDSS 6,0, spatial dissemination in the first RMN, system functional involved at onset, EDSS at last control, MSSS at last control.

Patients will then be classified on the basis of decades of diagnosis:

- 1983-1995: from the Poser criteria to the availability of the first immunomodulants
- 1996-2005: from the availability of the first immunomodulants to the onset of natalizumab (with subgroup 1996-2000 (McDonald's IFN Criteria) - 2001-205 (McDonald's Criteria - First Criterion Revision)
- 2005-2016: first and Second Revision of McDonald's Criteria (Subgroup 2005-2011: First McDonald-Second Revision Criteria Review and 2011-2016: Second Revision of Current McDonald Criteria).

DESCRIPTIVE EPIDEMIOLOGY

Jessica Frau
Centro Regionale per la Diagnosi e la Cura della SM, Ospedale R. Binaghi, ATS Sardegna, Università degli Studi di Cagliari, Cagliari

Evaluation of baseline prognostic factors in a large Italian cohort of patients with multiple sclerosis

The study of prognostic factors involved in the development and clinical course of multiple sclerosis (MS) has been and is still now of great interest. In the last decades, due to the improvement of diagnostic tools, not only clinical and demographic features, but also laboratory and radiological features have been considered as potential prognosis modifiers. To note, the introduction of DMDs in the early phase of MS, essentially due to the more precocious diagnosis due to the new diagnostic criteria, has been found to considerably impact the natural history of the disease. Thus, they could also have an effect on the historically considered prognostic factors.
The primary aim of the study is to evaluate in a large cohort of Italian MS relapsing patients the baseline prognostic factors, which can impact on the following outcomes: time to second clinical relapse, time to the achievement of the EDSS scores 3 and 6, MSSS score at the last follow-up. The analysis will be performed dividing the cohort in a group with diagnosis until 2000 and the other with diagnosis since 2001 until 2015. This cut-off has been chosen because coincident with application of the new diagnostic criteria and because it comes just few years after the introduction of DMDs. This could permit to understand whether the use of DMSs and the more precocious diagnosis impact on prognostic factors. Secondary outcome is to evaluate possible differences in prognostic factors between Sardinian patients and the other Italian cohort. Indeed, MS has a significant higher prevalence in the island, having a peculiar genetic and environmental background. Also in this case, both the Sardinian patients and the Italian cohort will be divided in 2 groups, in respect to the year of diagnosis (until 2000, and from 2001 until 2015) For each included subject the following features will be analysed: gender, age at onset, year of diagnosis, time from the onset to second relapse, functional systems involved at the onset, age at achievement of EDSS scores 3 and 6, MSSS at last follow-up, presence of oligoclonal bands IgG in cerebrospinal fluid, spatial dissemination in the first MRI.

DESCRIPTIVE EPIDEMIOLOGY

Paola Mosconi on behalf of Scientific Committee
Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano

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

In clinical practice and in clinical research, MS disability is measured through a standardized approach using the Expanded Disability Status Scale (EDSS). The prevention and the management of MS disability, as measured by the EDSS, is an important goal of clinical practice and clinical research. As suggested by recent literature, when referring to increases in MS disability the terms "worsening" and "progression" need to be distinguish: the term "worsening" describes increased disability due to relapses, while the term "progression" is reserved to progressively increasing disability unrelated to relapse activity. The use of a roving EDSS reference value should also allow more sensitive measurement of disability progression within relapse-free periods according to specific, time-based interval definitions (e.g., 24 or 48 weeks apart). This research project aims to evaluate/replicate and validate measures of disability progression unrelated to relapse using EDSS as proposed by Kappos et al, using data collected by the Italian SM as expression of real world setting.

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

INTEREST: Italian Multiple Sclerosis Registry Non interventional Retrospective Analysis in Secondary Progressive Multiple Sclerosis (SPMS)

Progressive forms of MS are characterized clinically by the accumulation of neurological disability, mostly independent of relapses and occurring from the initial disease course (primary progressive [PPMS]) or more commonly following an initial relapsing phase (secondary progressive [SPMS]). Distinguishing between relapsing and progressive phenotypes can be challenging: there is no biomarker differentiating the entities and the transition from relapsing to progressive phenotypes is only evident retrospectively (Lublin et al, Neurology. 2014). Evidence suggests that neurodegeneration, the main characteristic of the progressive phase, though initially triggered by inflammation, subsequently evolves independently, and that the CNS inflammation itself, though initially peripherally driven, becomes self-sustained. Consequently, MS therapeutic strategies should be stage-specific, which for progressive disease means directly controlling intrathecal inflammation, activating neuroprotective mechanisms, promoting remyelination/CNS repair (Lassmann et al,. Mult Scler. 2017). The aim of the study is to understand the epidemiology of SPMS and the current treatment practices in order to appropriately address the unmet needs, reduce cost and usage of ineffective therapies and manage the budget impact.

DESCRIPTIVE EPIDEMIOLOGY

Mario Alberto Battaglia on behalf of Scientific Committee
Fondazione Italiana Sclerosi Multipla, FISM, Genova

Validate a case definition of multiple sclerosis (MS) using different electronic (health and social) record: case study on selected provinces of Emilia Romagna Region

In recent years, there has been a growing interest in developing methods based on health administrative databases to estimate prevalence of chronic diseases and to assess quality in healthcare services. Health administrative data are attractive because of their relatively low cost, ease of use relative to other methods, and potential for repeated use over time. However, these data are not collected for research purposes, and their validity must be assessed before use. The objective of this study will be to validate a case definition of multiple sclerosis (MS) using multiple sources of health and social administrative data to provide estimates of MS incidence and prevalence for selected provinces of Emilia-Romagna region. Emilia-Romagna region Health Information Systems (HIS) will be the sources of health administrative data, while the database related to welfare and social security benefits (Istituto Nazionale della Previdenza Sociale, commonly known as INPS) will be that one of social administrative data. We will use population-based HIS and INPS database virtually available from January 1, 2008 to December 31, 2018 to identify individuals with MS using a potential case definitions. The algorithm sensitivity will test on a true-positive reference cohort of MS patients extracted from the Italian MS register. To test algorithm specificity, we will use a cohort of individuals who were presumably not affected by MS derived from the health administrative data. Besides, if a feasibility study will confirm the feasibility, we will use always to test algorithm specificity, a further reference group (true-negative) represented by subjects identified through the Italian MS Register as not affected by MS. Key point of the study will be the availability of clinical data (Italian MS Register) that will allow to evaluate the potential different degree of diagnostic accuracy between clinical and administrative data.

THERAPY OPTIMIZATION | Analysis of therapies

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

Assessing efficacy and safety of treatments in progressive Multiple Sclerosis

Background. The treatment of patients affected by Progressive Multiple Sclerosis (PMS) is controversial and these phenotypes are scarcely represented in RCTs. The European treatment guidelines give indications about the efficacy of Disease Modifying Drugs (DMDs) in Relapsing-Remitting Multiple Sclerosis, in Clinically Isolated Syndrome (CIS) and, as weak recommendation, in primary and secondary progressive multiple sclerosis (PPMS, SPMS). Instead, the North-American guidelines recommend considering discontinuing treatment with DMDs after the shift from the RR to the SP phase of the disease. The paucity of evidence based data on treatment strategies for PMS has many potential explanations: among these, the rarity of the PP course as compared with the RR one, the lack of drug whose mechanism of action is able to tackle the specific pathogenetic mechanisms and neurodegeneration that characterises PMS, the lack of sensitive and well-validated outcome measures assessing progression; inherent difficulties in the diagnosis of progression itself that remains mainly a clinical and retrospective one. At the same time, trial data about tolerability and safety of DMDs in PMS are limited as well. This is an extremely relevant issue: in fact, patients with PMS are usually older than those with RRMS and are at higher risk of age-correlated comorbidities. Moreover, a sizeable proportion of patients shift to the SP course after many years of immune-therapy.
In clinical practice, however, a considerable number of PPMS and SPMS patients are treated with first or second line DMDs, so that some information can be derived from the real-life population of patients included in MS registries.
The objective of the study is to provide real-life data about efficacy and safety of DMDs in PMS, compared with PMS not treated with DMDs. Secondary objectives of the present study are the comparison of results between patients with active PMS and non-active PMS and the comparison of results obtained in PMS using first and second line DMDs.
This is a multicentric, retrospective cohort study based on prospectively acquired data. Patients will be divided into 3 arms according with the treatment exposure during the PMS phase (PP or SP): 1) Patients taking first line DMDs 2) Patients taking second line DMDs 3) Patients taking no DMD (identified as reference or control group). Furthermore, within each group patients will be classified as having active or non-active disease (clinically and/or radiologically) using the Lublin and Reingold classification. To allow for a less biased comparison patients will be propensity score-matched according to disease duration, age, sex, EDSS score and previous therapies.
The primary efficacy endpoints are the annualized relapse rate, progression Index, time to 3- month CDP on the EDSS, time to discontinuation due to non-response. The primary safety end-points are frequency and severity of adverse events and time to discontinuation due to adverse events.

THERAPY OPTIMIZATION | Analysis of therapies

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

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

The present proposal is a large, multicentre, observational, retrospectively acquired cohort study, to evaluate the long-term impact of different treatment strategies on disability outcomes in patients with Relapsing MS (RMS) considering data on Italian IMedWeb MS Registry. Recent findings show the possibility that different treatment approaches may have similar long-term (at least 4 years) effects on disability progression in MS. Notably, the long-term impact of different treatment sequences is particularly relevant in specific conditions (e.g. women pursuing a pregnancy or pediatric patients), in which clinicians may need to postpone immunosuppressive therapies in favor of immunomodulatory drugs (such as IFN beta1a) with an improved risk/benefit ratio. Three groups of MS relapsing (RMS) patients will be evaluated from their first therapy: RMS subjects who started with IFN beta 1a SC 44 mcg switching to FTY, as first option, in treatment with FTY until the last follow-up, compared to RMS patients in treatment with FTY until the last follow-up and prescribed as first-line treatment (the oral drug with the longer follow-up) and patients who started with IFN beta 1a SC 44 mcg in treatment with IFN beta 1a SC 44mcg until the last follow-up.
This is an observational, retrospectively acquired cohort study. Longitudinal data will be extracted from the Italian iMedWeb MS Registry starting from 1st January 2010 (year of FTY market availability in Italy) to date, collected retrospectively. The time interval between IFN beta 1a 44 mcg cessation and switching to FTY will be considered as an untreated wash-out period. Patients with a wash-out period > or equal at 3 months will be not included in the analysis. To simulate a randomization, initial treatment effects were also explored by matching the treatment groups (IFN beta 1a 44 mcg SC or FTY) with a Propensity Score-based 1:1 matching algorithm.
Primary objective of the study is to evaluate the proportion of subjects with confirmed disability progression (CDP) between the three cohorts. A minimum of 3 visits (incl. baseline) at which an EDSS score has been recorded will be required, by definition, for a patient to be able to evaluate a confirmed disability progression event. EDSS scores recorded within 30 days after the onset of a relapse will be excluded.
Secondary objectives: Roving EDSS score in which the increase or decrease had to be separated from the last EDSS assessment by previous EDSS, the grow curves over time (from the initial treatment to last visit) of the estimated EDSS score, Annualized Relapse Rate (ARR), time to first on-treatment relapse. Additional objectives are on long term safety profile.

THERAPY OPTIMIZATION | Analysis of therapies

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

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

The treatment options for subjects with multiple sclerosis (MS) have expanded dramatically during the past 20 years. The objective of these disease-modifying treatments (DMTs) is the prevention of further relapses and accumulation of disability.
In the European Union neurologists and patients can currently choose from different licensed DMTs, six first-line and three second-line DMTs, making it increasingly difficult for patients and their physicians to choose between treatments at disease onset and in case of non-response to treatment. The aim of this study is evaluate the change in therapeutic approach with the availability of new first line oral drugs (teriflunomide and dimethyl fumarate - DMF). The study will compare the choice criteria to assign a specific DMT in naive and switching patients during the "old injectable era" and during the "first line orals and pegilations era". The main objectives of this analysis will be: to evaluate the determinants of the first treatment choice at the time of introduction of new therapies in a large Italian relapsing-remitting MS (RRMS) population; to evaluate the switch strategies after the first DMT discontinuation; to evaluate how the treatment choice is changed after the introduction of the new oral first-line drugs; to evaluate the tolerability and safety profile of the new DMTs This retrospective analysis will be divided into two phases and performed as follow: Two cohorts of RRMS patients will be evaluated separately. First, a retrospective cohort that includes all patients who started treatment as naive or switched their treatment during 24 months prior to the marketing of (i.e. AIFA approval date) the first oral drug first-line (teriflunomide). Second, a retrospective cohort of patients who started treatment as naive or switched treatment posterior to the marketing the first oral drug and covering an initiation or switching period of 12 months when all new drugs are available teriflunomide, DMF, pegylated interferon, alemtuzumab).
The primary analysis will be a description by a frequency distribution of first treatment choice in the enrolled population and of switch strategies. Baseline demographic, clinical and MRI data will be correlated with the DMT choice and timing. Heterogeneity among centres and geographic regions in the therapeutic approach will be evaluated. Chi square test will be used to assess heterogeneity among centres (anonymized) and multivariate logistic regression to evaluate the association of baseline factors with treatment choice.
Efficacy of DMTs will be assessed by the annualized relapse rate (ARR) and by the time to first relapse from treatment start and from treatment switch. Persistence on treatment will be evaluated by the Time to discontinuation. Safety will assess by the evaluation of the rate of the adverse event.

THERAPY OPTIMIZATION | Analysis of therapies

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

Big Multiple Sclerosis Data (BMSD) network

The project called BMSD network is a collaboration started in 2014 between the network of Italian multiple sclerosis (MS) centers, called iMedWeb network, subsequently merged into the Italian SM Register, 3 SM European registers (the Swedish, Danish and French registers) and the international MSBase network
The main objective of this collaboration is to try to solve key issues in MS research and patient management through large-scale data sharing. In the initial phase of the project, started in 2014 and concluded in the 2015, the technical feasibility of the project was verified.
A steering committee of the project has been appointed consisting of representatives of the 5 registers: Maria Trojano for the Italian SM Registry; Helmut Butzkueven for International MSBase database; Michel Clanet for the OFSEP of France; Melinda Magyari for the Danish MS Registry and Jan Hillert (sterring committee coordinator) for the Swedish MS Registry MS Registry. A data management sub-committee was also set up, which will be responsible for managing the phase of sharing the data from the 5 registers and analyzing the data. This working group is coordinated by Pietro Iaffaldano (Registro Italiano SM) and is made up of the data managers of each registry: Tim Spelman (MSBase); Nils Koch-Henriksen (Danish Registry); Leszek.Stawiarz (Swedish Registry); Roman Casey (OFSEP).
Three research projects have been elaborated, useful above all to test the possibilities of the global project. The objectives of the studies are: to evaluate the very long-term efficacy of early versus delayed DMTs treatment; to investigate the very long-term impact of DMTs on clinical disease progression in RRMS patients DMTs treated versus untreated RRMS patients and to evaluate the comparative long-term efficacy of first line DMTs - Injectables DMTs and Azathioprine.

THERAPY OPTIMIZATION | Analysis of therapies

Francesco Patti
Centro SM, AOU Policlinico Vittorio Emanuele Di Catania, Policlinico G. Rodolico, Catania

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

The aim of this Italian Pilot Study is to explore the feasibility of the retrospective approach for evaluating effectiveness in subjects previously treated with Cladribine and then followed as per clinical practice. The study results can inform on feasibility and identify modifications needed in a design of a larger, ensuing hypothesis testing study, where many different European Countries will be involved. The study will be conducted as a retrospective, observational study of patients with Clinically Isolated Syndrome (CIS) or Relapsing-Remitting Multiple Sclerosis (RRMS) treated with Cladribine as inclusions/exclusions criteria in the pivotal trials. This study aims to collect data on follow-up in clinical practice after Cladribine treatment, limited to patients recruited in Italian Centers. Data will be collected retrospectively through iMedWeb Database, which contains anonymous clinical data. The study period will be the time required for the abstraction of database for all patients. Data collection, using iMed database, is expected to last up to
approximatively 3 months following Study initiation. The source of information will be data collected from iMed database. Data will be entered into the electronic case report form by site staff. Approximatively 161 subjects are planned to be included. The analyses of this study will have two exploratory objectives: first, the feasibility of a large, retrospective study aimed at evaluating post-trial treatments and disease course in CIS/RRMS patients enrolled in randomized efficacy trials will be assessed. This assessment will be based on
the overall evaluation of the proportion of patients lost-to follow-up, and on quality and completeness of retrieved data. Second, the descriptive information obtained from this study on post-trial treatments and disease course will be valuable on its own, but will be also critical for the design of the large-scale observational study. In the analyses of the primary endpoint, Time to treatment change will be analysed by means of a classical Kaplan Meier Survival analysis, with start of a new therapy, treatment stop or death will be considered as events while survival times of patients lost to follow-up before starting a new therapy will be censored at the time of last information. This analysis will be complemented by a competing risk analysis, in which the reasons for treatment stop will be considered separately, using the Nelson-Aalen estimator of the cause-specific cumulative hazards: the cumulative incidences of the following competing reasons for treatment stop will be computed: start of a new therapy, no further treatment (after one year since last Cladribine course, death, unknown).

THERAPY OPTIMIZATION | Analysis of therapies

Emanuele D'Amico
Centro SM, AOU Policlinico Vittorio Emanuele Di Catania, Policlinico G. Rodolico, Catania

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

Real-world studies about effectiveness of initial disease-modifying treatment (DMT) choices for relapsing-remitting multiple sclerosis (RRMS) are scarce.
This study aims to assess the effectiveness and drug discontinuation rates of new first DMT choices among patients with newly diagnosed RRMS.
This will be a retrospective cohort study used prospectively collected data. Centers specialized in MS care will be invited to join the project. The MS centers are settled in Italy and they are recognized by the Italian registry for MS. Patients with RRMS who received diagnoses from January 1, 2010, to December 31, 2015 will be identified and will be considered to enter the study. Outcomes will include annualized relapse rate (ARR), proportions relapse free, confirmed progression free, proportions neuroradiological activity free, treatment persistence, discontinuation of therapy due to any reason.

Matilde Inglese
Centro per lo Studio e la cura della SM e Malattie Demielinizzanti – DiNOGMI, Ospedale Policlinico San Martino, Genova

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

Following twenty years of experience, autologous hematopoietic stem cell transplantation (aHSCT) is now an accepted treatment for aggressive multiple sclerosis (MS). The first studies mainly focused on treatment-refractory secondary-progressive (SP) MS patients, but the evidence of the extraordinary anti-inflammatory activity of the procedure has promptly shifted the use of aHSCT to aggressive relapsing-remitting MS.
However, beyond the profound effect on relapses and MRI inflammatory activity, some studies have also suggested that aHSCT could be able to prevent long-term neurological deterioration in established progressive MS patients. Indeed, recent evidence suggests that targeting inflammation might reduce accrual of neurological disability even in progressive MS patients, as suggested by recent studies of B-cells targeted drugs and sphingosine 1-phosphate receptor modulators in SPMS. Given the paucity of available therapeutic options for SPMS, it's of fundamental importance to evaluate the long-term effect of aHSCT in preventing disability progression in SPMS. We therefore planned this retrospective multicenter observational study in order to compare disease progression between patients with SPMS who were treated with aHSCT in six Italian MS centers and matched controlled patients with SPMS reported in the Italian MS Register.

THERAPY OPTIMIZATION | Specific Project

Francesco Patti
Centro SM, AOU Policlinico Vittorio Emanuele Di Catania, Policlinico G. Rodolico, Catania

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

Physicians treating patients with multiple sclerosis (MS) are consistently attempting to balance the risks and benefits of all medications available for MS treatment. In particular, natalizumab (NTZ) treatment has exhibited a substantial reduction in both clinical and radiographic evidence of disease activity in several clinical trials even though it is associated with a potentially fatal complication by reactivation of latent JC virus (JCV), progressive multifocal leukoencephalopathy (PML). This retrospective multicentre study answers the question what clinical effect extended interval dosing (EID) schedules of NTZ has on managing MS. Indeed, the main objective of this study is to evaluate the effectiveness and safety of NTZ when is administered according the extended dosing strategy compared to standard scheduled administration.
All relapsing-remitting MS patients eligible for the study will be stratified into four groups based on NTZ treatment schedule received: standard interval dosing (SID) including patients who received infusions on average every 28-34 days; intermediate late extended dosing (ILED) including patients who have been infused on a schedule every 35 -41 days; late extended dosing (LED) including patients infused on a schedule every 42-48 days; very late extended dosing (VLED) including patients infused on a schedule higher than 48 days. We will collect using iMed software the following data: demographic characteristics, clinical data about MS (time to reach EDSS 4.0 and 6.0, symptoms and signs at onset and at follow-up visits, EDSS scores at onset and at last visit, comorbidity, total number of relapses, number of relapses in the year before NTZ and during NTZ, immunomodulant exposure prior to NTZ, immunosuppressive exposure prior to NTZ); NTZ treatment data (start date NTZ, number of doses administered, reason of discontinuation: progressive multifocal leukoencephalopathy concern, pregnancy, adverse event, patient's choice or lack of efficacy of the natalizumab treatment), JCV status at NTZ treatment onset and at last follow-up, PML (date of onset, symptoms at onset, type of treatment, number of NTZ administered before onset of PML, outcome, MRI data at PML diagnosis), MRI data at diagnosis and at follow-up visits. A multivariate Poisson regression model accounting for overdispersion will be used to assess incidence of relapses in the 4 groups during NTZ treatment, whereas multivariate Cox proportional hazards regression was used to model the time to reach the 1st relapse and EDSS score 4 and 6. All the models will be adjusted for the baseline covariates. Furthermore, to allow for an unbiased comparison, these patients will be propensity score-matched on a one-to-one basis.

THERAPY OPTIMIZATION | Specific Project

Matilde Inglese
Centro per lo Studio e la cura della SM e Malattie Demielinizzanti – DiNOGMI, Ospedale Policlinico San Martino, Genova

The concept of persistence in disability improvement: an application of Markov model to treated patients from the Italian Registry

The concept of EDSS improvement due to a treatment has been recently introduced in MS studies for patients treated with highly effective therapies. Some drugs showed not only an effect in reducing the risk of EDSS progression, but resulted able to induce an EDSS improvement. Recently, a prospective study conducted on about 5000 RRMS patients treated with Natalizumab, revealed a mean regression of EDSS up to 5 years of follow-up and the probability of EDSS improvement (27% at 5 years) was higher than the progression rate (14% at 5 years). Other real world studies, compared, among other outcomes, the probability of EDSS improvement in patients treated with Natalizumab vs Fingolimod. Both studies reported a significant difference between the two treatments in favour of Natalizumab with a higher sustained rate of EDSS improvement. An important issue not addressed when examining the probability of EDSS improvement is how long the patient maintains the improvement status as compared with pretreatment EDSS levels.
The main aim of this research project is to develop statistical methods to quantify and test the insurgence and the persistence of EDSS improvement, using data from a cohort of patients treated with Natalizumab extracted by the Italian Registry. We will select a control group of patients treated with Fingolimod to set up a hypothesis test assessing whether the persistence of improvement is significantly different between two groups.
The choice of developing this methodology on Natalizumab treated patients is based on previous data showing that this treatment is able to induce an improvement in MS patients. In the first phase all RRMS of age >18 years included in the Registry and who are treated with Natalizumab or Fingolimod will be extracted. All demographic and clinical characteristics (Age, EDSS, disease duration, relapse status pretreatment) present in the minimum dataset of the registry will be used. In the second phase, data will be analysed by mean of Markov models using Stata and R. The expected result is the development of a statistic to quantify the prevalence of improved patients over time, the quantification of its confidence intervals and a statistical test to compare this prevalence curve between groups.

THERAPY OPTIMIZATION | Prognostic factors and predictive models of therapy response

Roberto Bergamaschi
Centro SM, Fondazione Istituto Neurologico Nazionale Casimiro Mondino, Pavia

Early prediction of unfavorable evolution of Clinically Isolated Syndrome (CIS) patients. RECIS (Risk Estimate for CIS) study

This multicenter project aims to define prognostic models for the prediction of losing NEDA status in CIS patients, through the analysis of a large set of clinical and instrumental variables (MRI, evoked potentials, cerebrospinal fluid) collected in CIS patients.
We include in the analysis the records of 357 patients from 4 MS Center (Bari 110; Firenze 103; Gallarate 48; Pavia 96) selected on the basis of the following criteria: clinically isolated syndrome; first neurological evaluation within three months from onset; first MRI examination suggestive for MS within one months from first neurological evaluation.
In order to define prognostic models for the prediction of losing NEDA status in CIS patients, we will characterize all the patients enrolled on the basis of their different "propensity" to reach the unfavourable end-point, by fitting predictive models based on frequentist and on Bayesian approaches. We used a multiple multinomial logit model and an information theoretical approach to preliminary analyze the records of 76 patients in order to obtain a prognostic model for the risk of losing NEDA status. Patients losing NEDA were 59 (77%): 31 at 6 months, 14 at 12, and 14 at 24 months. We are in process to analyze all the collected records (357 patients); develop the best prognostic model, comparing Bayesian and frequentist approaches; setting up of a personalized prognostic score and validate of the prognostic model and of the individual prognostic score on different data set.

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

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

Multiple Sclerosis (MS) is a disease characterized by clinical relapses, however scientific evidences underline the presence of a disease progression independent from relapses, which could occur also in patients under treatment.
The present study aims at evaluating the rate over time of disability progression and the factors associated to the disability progression unrelated to relapse in a real world setting.
The study foresee the extraction and analysis of data collected within the FISM Registry from its constitution to 2017.

THERAPY OPTIMIZATION | Prognostic factors and predictive models of therapy response

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

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

Higher-efficacy disease modifying therapies (DMTs) for multiple sclerosis (MS), such as natalizumab, alemtuzumab, mitoxantrone or fingolimod, have a consistently superior effect on disease activity than firstline MS therapies, such as interferon ß.
To date, the most applied treatment algorithm is based on the escalation strategy, initiating treatment with one of the registered first-line DMTs (interferon ß, glatiramer acetate, teriflunomide or dimethilfumarate) and escalating to a higher-efficacy agent in patients who experience on-treatment relapses or progression of disability.
Whether patients initiating higher-efficacy DMTs as their first therapy derive a greater benefit from treatment than those who start with the first-line agents, remains a matter of debate. Indirect comparisons from extension arms and subgroup analyses of randomized trials suggest that higherefficacy therapies are associated with improved control of relapse activity when initiated earlier after MS onset.
However, the effect of timing on the effectiveness of therapies on disability outcomes is still to be clarified. Using the global Italian Multiple Sclerosis Registry cohort, we will evaluate the comparative efficacy on relapse and disability outcomes in patients who commenced one of four higher-efficacy DMTs (natalizumab, alemtuzumab, mitoxantrone, fingolimod) as their first treatment and in patients who started their treatment history with the first-line agents (interferon ß, glatiramer acetate, teriflunomide or dimethilfumarate).

THERAPY OPTIMIZATION | Prognostic factors and predictive models of therapy response

Marzia Romeo
Centro SM, Ospedale San Raffaele, Milano

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

Multiple sclerosis (MS) is one of the most common cause of neurological disability in young adults globally. It is a chronic degenerative illness and therefore carries a high economic and quality of life burden associated with it. One of the principal objectives in the care of people with MS is, therefore, to reduce the irreversible accumulation of neurological disability. The diagnosis of progressive MS is clinical and retrospective because based on the patient's history and the neurological exam. In everyday clinical practice, the identification of the change in disease course is often late and there are no applicable predictors of disability progression. Therefore, the objective of the present study is to identify the predictive factors of disability progression in patients with progressive course of MS included in the datasets of the Italian MS registry. The population of the Italian MS registry is representative of MS population of our Country and includes a large number of patients. This is a retrospective longitudinal study enrolling patients with secondary progressive MS (SP-MS), primary progressive MS (PP-MS) and relapsing-remitting MS (RR-MS) with Expanded Disability Status Scale (EDSS) > 4.0 and without disease activity (clinical and MRI) in the previous 6 months. A 2-year follow-up is required. The outcome of the three groups of patients, defined as disability progression sustained for at least 6 months and confirmed at the end of the 2 years' follow-up, will be compared in order to identify demographic, clinical and brain MRI variables predictive of disability progression. The early identification of patients with unfavorable predictive variables will allow treating patients with the new coming soon therapies for MS (ocrelizumab and siponimod).

RARE FORMS OF MS

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

E-MUSIC: Early MUltiple Sclerosis Italian Cohort

This multicentric project aims to identify a cohort of Italian MS patients presenting with a first clinical episode suggestive for MS and prospectively follow them in a standardized manner. This cohort will constitute a meeting point for all the MS Italian centres for study proposals, especially large observational studies with various objectives.
The aim of this first project is to evaluate if and how the prognostic indicators vary in 3 subgroups of patients with different age at onset: Pediatric Onset Multiple Sclerosis (POMS, age at onset = 18 years), Adult Onset Multiple Sclerosis (AOMS, age at onset from 18 and 49 years) and Late Onset Multiple Sclerosis (LOMS, age at onset = 50 years). The outcomes of the study will be: a) time to conversion from clinically isolated syndrome (CIS) to clinically defined MS (CDMS) or from the I to the II clinical episode (for those who fulfil the McDonald's 2010 criteria from the first episode); b) time to a first confirmed EDSS worsening at 3 months. The single prognostic indicators will be distinguished in high, medium and low risk predictors on the basis of the data obtained from the statistical analysis.

Methods. This is a multicentric, retrospective study based on prospectively acquired data (type 1 study) on patients followed from their first clinical episode from January 1st, 2008.
Possible predictors that will be analysed are: age at onset (POMS, AOMS, LOMS), sex, disease course (primary progressive or relapsing remitting), familiarity for MS (first or second degree relatives), comorbidities, number/type of functional system involved, topography of first clinical episode (monofocal if the clinical presentation is with an Isolated Optic Neuritis, Isolated Spinal Syndrome, Isolated Supratentorial Syndrome -ADEM-like onset included- or Isolated brainstem Syndrome; will be termed multifocal if two or more of the abovementioned systems are involved), number of lesions at MRI scan, presence of intrathecal Oligoclonal Bands (OB) at the Cerebrospinal Fluid (CSF), the exposition and type of Disease Modifying Drugs (first - or second - line DMDs) and time to a first DMD. Furthermore, the tolerability, safeness and response to the first DMD in term of safeness and efficacy will be analysed.

RARE FORMS OF MS

Damiano Baroncini
Centro SM di Gallarate, ASST della Valle Olona, Busto Arsizio, VA

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

Pediatric onset multiple sclerosis (POMS) is currently reported in about 3–10% of all MS subjects1. Compared to adults, the large majority of patients present a higher disease activity, but also a greater capability of recovery2 as they reach mild and severe disability after a longer time, in spite of the higher relapse rate. However, this does not mean that POMS has a better prognosis as mild and severe disability is reached at a lower age2. For these reasons, guidelines suggest to start disease modifying treatments (DMTs) as soon as possible3. DMTs in POMS have been evaluated in small, short-term observational studies showing a similar safety and efficacy compared to adults4. Recently, one study showed that DMTs exposure delayed disability worsening in pediatric patients with an isolated demyelinating event5. It has been shown that the clinical outcome is better starting earlier and using more effective drugs6 and that the effect of DMTs could be more pronounced in subject treated before 12 years of age7. These results suggest that long-term prognosis, in particular disability accumulation, should have been positively changed after the introduction of DMTs. However, there are no objective and long-term data to confirm this hypothesis. The aim of this study is to evaluate if clinical course of POMS patients has been significantly modified after the introduction of DMTs in clinical practice, in a large cohort of MS patients. Moreover, we will try to identify some early predictors of disability accumulation in this population.

INDEX

Specific Project

Prognostic factors and predictive models of therapy response

RARE FORMS OF MS

www.registroitalianosm.it