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Authors: Alice Laroni, MD, PhD; Alessio Signori, PhD; Giorgia T. Maniscalco, MD ; Roberta Lanzillo MD, PhD; Cinzia Valeria Russo, MD; Eleonora Binello, MD; Salvatore Lo Fermo, MD; Annamaria Repice, MD; Pietro Annovazzi, MD; Simona Bonavita, MD; Marinella Clerico, MD, PhD; Damiano Baroncini, MD; Luca Prosperini, MD, PhD; Sara La Gioia, MD; Silvia Rossi, MD, PhD; Eleonora Cocco, MD; Jessica Frau, MD; Valentina Torri Clerici, MD; Elisabetta Signoriello, MD; Arianna Sartori, MD; Ignazio Roberto Zarbo, MD; Sarah Rasia, MD; Cinzia Cordioli, MD; Raffaella Cerqua, MD; Alessia Di Sapio, MD; Luigi Lavorgna, MD; Simona Pontecorvo, MD, PhD; Caterina Barrilà, MD; Francesco Saccà, MD; Barbara Frigeni, MD; Sabrina Esposito, MD; Domenico Ippolito, MD; Fabio Gallo, MSc; Maria Pia Sormani PhD; On behalf of the iMUST group

Alice Laroni, University of Genova, Department Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Center of Excellence for Biomedical Research (CEBR), IRCCS San Martino-IST, Genova, Italy

Alessio Signori, Department of Health Sciences, Section of Biostatistics, University of Genova, Italy

Giorgia T. Maniscalco, Neurological Clinic and Multiple Sclerosis Centre of "AORN A.Cardarelli" , Naples, Italy

Roberta Lanzillo, Department of Neurosciences, Reproductive Sciences and Odontostomatology, Multiple Sclerosis Centre, Federico II University, Naples, Italy

Cinzia Valeria Russo, Department of Neurosciences, Reproductive Sciences and Odontostomatology, Multiple Sclerosis Centre, Federico II University, Naples, Italy

Eleonora Binello Centro SM, Dipartimento di Neuroscienze, Ospedale Universitario Città della Salute e della Scienza di Torino, Italy

Salvatore Lo Fermo, Neurological Clinic A.O.U. Policlinico Vittorio Emanuele, Catania, Italy.

Annamaria Repice, 2nd Neurology Unit and CRRSM (Regional Referral Multiple Sclerosis Centre),Careggi University Hospital, University of Florence, Italy.

Pietro Annovazzi, Multiple Sclerosis study center, ASST Valle Olona, PO di Gallarate (VA), Italy.

Simona Bonavita, Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Second University of Naples, Italy

Marinella Clerico , Clinical and Biological Sciences Department, Neurology Unit, University of Torino, San Luigi Gonzaga Hospital, Orbassano, Torino, Italy

Damiano Baroncini, Multiple Sclerosis study center, ASST Valle Olona, PO di Gallarate (VA), Italy.

Luca Prosperini, Dept. of Neurology and Psychiatry, Sapienza University, Rome, Italy

Sara La Gioia, Centro Sclerosi Multipla ASST Papa Giovanni XXIII di Bergamo, Italy

Silvia Rossi, Neuroimmunology and Neuromuscolar Diseases Unit, IRCCS Foundation Carlo Besta Neurological Institute, Milan, Italy.

Eleonora Cocco, Dpt Medical Science and Public Health, University of Cagliari, Italy,
Jessica Frau, Dpt Medical Science and Public Health, University of Cagliari, Italy
Valentina Torri Clerici, Neuroimmunology and Neuromuscolar Diseases Unit, IRCCS Foundation Carlo Besta Neurological Institute, Milan, Italy
Elisabetta Signoriello, Multiple Sclerosis Center, II Division of Neurology, Second University of Naples
Arianna Sartori, Neurology Clinic, Department of Medical, Surgical, and Health Sciences, University of Trieste, Italy,
Ignazio Roberto Zarbo, Department of Clinical and Experimental Medicine, University of Sassari, Italy.
Sarah Rasia, Multiple Sclerosis Center, ASST Spedali Civili, PO di Montichiari (BS), Italy.
Cinzia Cordioli, Multiple Sclerosis Center, ASST Spedali Civili, PO di Montichiari (BS), Italy.
Raffaella Cerqua, Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona , Italy
Alessia Di Sapio 2nd Neurology Unit and CReSM (Regional Referral Multiple Sclerosis Centre), AOU San Luigi Gonzaga, Orbassano, Torino, Italy.
Luigi Lavorgna Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Second University of Naples, Italy
Simona Pontecorvo, Dept. of Neurology and Psychiatry, Sapienza University, Rome, Italy.
Caterina Barrillà, Department of Neurology, Valduce Hospital, Como.
Francesco Saccà, Department of Neurosciences, Reproductive Sciences and Odontostomatology, Multiple Sclerosis Centre, Federico II University, Naples, Italy
Barbara Frigeni, Centro Sclerosi Multipla ASST Papa Giovanni XXIII di Bergamo, Italy
Sabrina Esposito, Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Second University of Naples, Italy
Domenico Ippolito, Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Second University of Naples, Italy
Fabio Gallo, Department of Health Sciences, Section of Biostatistics, University of Genova, Italy
Maria Pia Sormani Department of Health Sciences, Section of Biostatistics, University of Genova, Italy

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Corresponding author:
Maria Pia Sormani
Department of Health Sciences (DISSAL)
University of Genova
Biostatistics Unit
Via Pastore, 1 16132
City name GENOVA
Phone +39-010-3538473

Alice Laroni, alice.laroni@unige.it
Alessio Signori, alessio.signori@medicina.unige.it
Giorgia T. Maniscalco, gtmaniscalco@libero.it
Roberta Lanzillo, robertalanzillo@libero.it
Cinzia Valeria Russo cinziavaleria@hotmail.it
Eleonora Binello, eleonora.binello@virgilio.it
Salvatore Lo Fermo, totolof@hotmail.com
Annamaria Repice, annamaria.repice@libero.it
Pietro Annovazzi, pietro.annovazzi@gmail.com
Simona Bonavita, simona.bonavita@unina2.it
Marinella Clerico, marinella.clerico@unito.it
Damiano Baroncini, damianobaroncini@gmail.com
Luca Prosperini, luca.prosperini@gmail.com
Sara La Gioia, saralagioia@yahoo.it
Silvia Rossi, silvia.rossi@istituto-besta.it
Eleonora Cocco, ecocco@unica.it
Jessica Frau, jessicafrau@hotmail.it;
Valentina Torri Clerici, valentina.torri@istituto-besta.it
Elisabetta Signoriello, elisabetta.signoriello@gmail.com
Arianna Sartori, sartoriarianna23@gmail.com
Ignazio Roberto Zarbo, robertozarbo@gmail.com
Sarah Rasia, sarah.rasia@gmail.com
Cinzia Cordioli, cinzia.cordioli@gmail.com
Raffaella Cerqua, cerquaraffaella@libero.it
Alessia Di Sapio adisapio2210@gmail.com
Luigi Lavorgna Luigi.Lavorgna@policliniconapoli.it
Simona Pontecorvo, simonapontecorvo@yahoo.it

Caterina Barrillà, caterina.barrila@gmail.com
Francesco Saccà, francesco.sacca@unina.it
Barbara Frigeni, barbarafrigeni@hotmail.com;
Sabrina Esposito, sabryesposito84@gmail.com
Domenico Ippolito mimmo-leone88@hotmail.it
Fabio Gallo, fabio.gallo@unige.it
Maria Pia Sormani, mariapia.sormani@unige.it

Statistical analysis conducted by: Maria Pia Sormani, Alessio Signori

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Author contributions

Alice Laroni proposed the project, acquired the data, participated in data analysis and interpretation, and wrote the manuscript.
Alessio Signori: managed, analyzed and interpreted the data and contributed to manuscript draft.
Giorgia T. Maniscalco, acquired the data, participated in data analysis and interpretation, contributed to manuscript draft.
Roberta Lanzillo acquired the data, participated in data analysis and interpretation, contributed to manuscript draft.
Cinzia Valeria Russo acquired the data, participated in data analysis and interpretation, contributed to manuscript draft.
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Pietro Annovazzi acquired the data, participated in data analysis and interpretation, contributed to manuscript draft.
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Raffaella Cerqua acquired the data, participated in data analysis and interpretation, contributed to manuscript draft.

Alessia Di Sapio acquired the data, participated in data analysis and interpretation, contributed to manuscript draft.

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Barbara Frigeni, acquired the data, participated in data analysis and interpretation, contributed to manuscript draft.

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Sara La Gioia Nothing to disclose

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Abstract

Objective To assess whether the presence of concomitant diseases at multiple sclerosis (MS) diagnosis is associated to the choice and the treatment persistence in an Italian MS cohort.

Methods We included newly diagnosed patients (2010-2016) followed in 20 MS centers, and collected demographic and clinical data. We evaluated baseline factors related to the presence of comorbidities, and the association between comorbidities and the clinical course of MS and the time to the first treatment switch.

Results The study cohort included 2076 patients. Data on comorbidities were available for 1877/2076 patients (90.4%). 449/1877 (23.9%) patients had at least one comorbidity at MS diagnosis. Age at diagnosis (OR = 1.05, 95% CI 1.04-1.06; p<0.001) was the only baseline factor independently related to the presence of comorbidities. Comorbidities were not significantly associated with the choice of the first disease-modifying treatment, but were significantly associated to higher risk to switch from the first treatment due to intolerance (HR 1.42, CI 1.07-1.87, p= 0.014). Association of comorbidities with risk of switching for intolerance was significantly heterogeneous among treatments (interferon-beta, glatiramer acetate, natalizumab or fingolimod, interaction test, p= 0.04).

Conclusions Comorbidities at diagnosis should be taken into account at the first treatment choice because they are associated to lower persistence on treatment.

Introduction

Despite a therapeutic scenario of increasing variety, personalized medicine for multiple sclerosis (MS) is still an unmet need. Phase II and phase III clinical trials with new drugs for MS are conducted in highly selected patient populations, with "ideal" characteristics, which include the absence of concomitant diseases and/or medications[1] . However, 40 to 66% of MS patients have at least one additional disease [2] [3], which may affect the response to disease-modifying drugs (DMDs) . For this reason, a more accurate characterization of comorbidities in MS and the study on their effect on MS outcomes haves been recommended[4]. A recent

series of review articles suggested that MS patients may have a specific pattern of comorbidities[5 6]. Comorbidities have been associated to older age at MS diagnosis, higher disability, diagnostic delay [7] , increased hospitalization[8], and increased mortality [9]. However, no studies pointed to the association of comorbidities with the efficacy or safety of DMDs.

On these bases, our aim was to assess 1) the prevalence of comorbidities at MS diagnosis in a large sample of Italian MS patients 2) whether MS patients with comorbidities have different clinical characteristics at diagnosis; 3) whether comorbidities at diagnosis may be associated to the DMD choice; 4) whether comorbidities at MS diagnosis may be associated to treatment persistence, and 5) whether comorbidities are correlated to the accumulation of disability

Methods

We retrospectively enrolled patients followed up longitudinally in 20 MS centers in Italy. The study was approved by the ethics committee of the coordinating center (Genova) and the original raw data collections were approved by the local ethics committees at all centers and written informed consent was obtained from all study patients. The main inclusion criteria were diagnosis of MS since 2010, according to the 2005 and 2010 revisions of the McDonald criteria [10 11] and starting a DMD within one year from diagnosis.

We collected anonymized demographic and clinical data, presence/absence of comorbidities at diagnosis, name and date of first DMD, date and reason for switch- classified as inefficacy or intolerance (the latter including side effects, pregnancy, patient decision), and EDSS at last follow-up. Such classification was meant to differentiating switches due to inefficacy from all other reasons for switch. Patients without data on presence of comorbidities were excluded from the analysis. For data collection, neurologists extracted the data from the databases of local MS centers, and statisticians merged them in a unified database, and ran the data quality control. Neurologists entered data regarding patients that were in their care, thus ensuring completeness. As second step, data regarding all patients identified as having comorbidities were reviewed in order to classify the comorbidities and patients were recalled in case of missing data. Comorbidities were classified according to the series of review papers within the special issue of Multiple Sclerosis Journal: "International Workshop on Comorbidities in MS", [5, 12-18] with some changes. To ensure standardization,

classification was discussed and agreed upon by the participating neurologists and statisticians in an ad-hoc Investigators'meeting.

We evaluated baseline factors (age, sex, education, time between onset and diagnosis, Expanded Disability Status Scale -EDSS-, presence of active lesions at brain and/or spinal cord MRI) associated with comorbidities and association of comorbidities with first therapy choice by logistic regression adjusted for center and year of diagnosis. The multivariable model was built including all variables that resulted significant at the univariable analysis. The association of comorbidities with time to switch during follow-up was assessed by a multivariate Cox model adjusted for baseline characteristics (i.e. aAge at diagnosis, year of diagnosis and center), with time origin being time at which treatment was initiated. In order to assess whether the association of comorbidities with the probability to switch was different among therapies, an interaction test was used.

The association of specific comorbidities with time to switch was also investigated including the variable into the multivariable Cox model.

The relationship of comorbidities with the EDSS change at the last follow-up was evaluated by a non-parametric analysis of covariance, adjusting for length of follow up, age at diagnosis, baseline EDSS, first treatment choice, and persistence on treatment. A p-value lower than 0.05 was considered statistically significant. Stata (v.13; StataCorp.) was used for the computation.

Results

1. **Study cohort**

The study cohort included 2076 patients. The proportion of patients included in the study among the newly diagnosed patients across the 20 centers, that had provided written permission of use of anonymized personal clinical data for research purposes, was highly variable (median 40% , range 10%-100%), depending on the number of neurologists from each center involved in the study, and the center size. Data on comorbidities were available for 1877/2076 patients (90.5%), that were included in this analysis. **Table 1** reports the baseline demographic and clinical characteristics of these patients. Briefly, mean age at diagnosis was 35.3

years (SD: 11.3), females were 1218 (64.9%) and median time between disease onset and diagnosis was 0.82 years (IQR 0.23-3.41). Patients were followed in median for 2.6 years.

Four hundred and forty-nine (23.9%) patients had at least one comorbidity at MS diagnosis. At multivariate analysis, age at diagnosis (adjusted OR=1.05, 95% CI 1.04-1.06; p<0.001) was the only baseline factor independently related to the presence of comorbidities (**Table 1**).

Ninety-eight (5.2%) patients had at least 2 comorbidities at MS diagnosis. Mean age at diagnosis was 44.8 years (SD 11.4) in those with more than one comorbidity compared to 38.7 (SD 10.9) in those with one comorbidity (p<0.001).

2. Prevalence of specific comorbidities at diagnosis

Comorbidities categorized by affected system are listed in **Table 2**. In detail, 7.2 % patients had at least another autoimmune disease and 0.3 % had at least two additional autoimmune diseases. Most common autoimmune diseases were autoimmune thyroid disease (85/136, 62.5%), type 1 diabetes mellitus (16/136, 11.8%) and celiac disease (12/136, 8.8%).

5.3% of patients had a psychiatric comorbidity at MS diagnosis, and 0.3 % had at least two psychiatric comorbidities. Most common psychiatric diseases were depression (N =53/99, 53.5%), anxiety (N= 17, 17.2%) and bipolar disorder (N= 11, 11.1%).

5.1% of patients had at least one cardiovascular disease and one patient had at least two cardiovascular diseases. Most common cardiovascular diseases were arterial hypertension (86/96, 89.6%) and cardiac arrhythmias (3/96, 3.1%).

2.8% of patients had at least one other metabolic diseases (including type 2 diabetes mellitus) and 0.2% had at least two metabolic diseases. Most common metabolic diseases were hyperlipidemia (34/52, 65.4%) and type 2 diabetes mellitus (12/52, 23.1%).

2.3% of patients had at least one other neurologic disease and 0.05% had at least two other neurologic diseases. Most common other neurologic diseases were: migraine (31/44, 70.4%), other types of headache (4/44, 9.1%), and epilepsy (7/44, 15.9%).

Demographics and clinical data among those with specific comorbidities are detailed in **Supplemental Table 1.**

3. Association of choice of the first DMD with comorbidities

First treatment included: interferon-beta (IFN-β) 1a 22-44 µg subcutaneously (sc) (N=588; 31.8%), IFN-β 1a 30 µg intramuscularly (im) (N= 323, 17.5%), IFN-β 1b 250 µg sc (256, 13.8%), glatiramer acetate (GA) (N=299;16.2%), natalizumab (N=129; 7%), dimethylfumarate (N= 90, 4.9%), fingolimod (N=75; 4.1%), teriflunomide (N= 36, 2.0%), other/unspecified treatments (N=81; 4.3%).

Heterogeneity in proportion of patients with comorbidities according to treatment groups (**Figure 1**) was detected (p=0.013). In detail, we observed a higher frequency of patients with concomitant diseases among those treated with GA (30.4%), dimethylfumarate (30%), and teriflunomide (44.4%). However, after adjusting for age at diagnosis, year of diagnosis, and center, no significant differences according to treatment group were observed (p=0.59).

4. Association of comorbidities with the switch from the first treatment

Almost half of treated patients (Kaplan-Meier estimation=47.7%) switched therapy after three years. Cumulative incidence of treatment switch due to inefficacy at three years was 26.4%, and cumulative incidence of switch due to intolerance was 18.9%. Pregnancy was the reason of 12 (4%) and risk of PML was the reason of 33 (11%) out of 297 intolerance-driven switches . Cox regression analysis, adjusted for baseline characteristics (age at diagnosis, year of diagnosis, center) and first DMD, showed that comorbidities did not affect the first treatment switch due to inefficacy (HR 1.19, 95 % CI 0.92-1.55, p= 0.19), but had a significant effect on the switch due to intolerance (HR 1.42, CI 1.07-1.87, p= 0.014).

Therefore, we focused the analysis on the association of comorbidities with intolerance-switch from specific DMDs. We restricted this analysis to interferon-beta, GA, natalizumab (which were all available in Italy before 2010) and fingolimod (which was became available in Italy at the end of 2011 and could be prescribed since the beginning of the same year in the context of an open label study, the study CFTY720DIT03), since dimethylfumarate and teriflunomide had a too-short follow up to draw reliable

conclusions. We found a significant interaction between comorbidities and first DMD on the probability to switch due to intolerance (p= 0.04), indicating that comorbidities had a different relationship with the probability to switch according to the first DMD. An increased risk of intolerance switch is confined to patients treated with IFN-β, while comorbidities were not associated with the probability to switch in patients treated with GA, natalizumab or fingolimod (**Figure 2**). However, in patients with IFN-β as their first DMD there was no evidence of an association between specific comorbidities and the probability to switch due to intolerance (p=0.96).

5. Relationship of comorbidities with disability at follow up

Mean EDSS change at last follow up, was 0.28 (SE=0.05) for patients with comorbidities and 0.10 (SE=0.03) for those without comorbidities (Supplemental figure 1). The difference, after adjusting for follow up duration, baseline EDSS, center, age at diagnosis, year of diagnosis, and first DMD and at least one switch during follow up, in a multivariate nonparametric analysis of covariance, was statistically significant (p=0.018)

Discussion

This retrospective study provides new evidence on the burden of comorbidities at MS diagnosis and reveals that comorbidities increase the risk of switching from the first DMD due to intolerance, particularly when the first DMD is IFN-β.

Previous studies have reported data on incidence and prevalence of comorbidities throughout MS disease course. A study on 8983 patients enrolled in the North American Research Committee on Multiple Sclerosis (NARCOMS) registry, a self-reported registry for MS patients, found that almost 40% of patients with MS have a concomitant medical condition, with higher prevalence in males, older patients, African American patients, and those with lower income[2]. In the same patient cohort, specific comorbidities were associated to longer time between disease onset and diagnosis (diagnostic delay), and partly to self-reported disability at diagnosis[7]. There are few data regarding the prevalence of comorbidities at MS diagnosis. A

French study on the National health care data, including 22087 MS patients, reported that about 5% had a registered comorbidity diagnosed before or after MS[19].

Compared to these studies, we employed a retrospective approach to analyze the prevalence of neurologist-reported comorbidities at MS diagnosis in a cohort of patients diagnosed from 2010 to 2016. We estimate that patients enrolled in this study are a representative sample of the Italian MS population, including almost 10% of the newly diagnosed patients in Italy in the timeframe of enrollment (given an approximate incidence of 3400 new cases/year in Italy- http://www.aism.it/index.aspx?codpage=2016_05_stampa_sn_barometro_sintesi) and because centers from all geographic zones of Italy were enrolled in this study.

We found that about one out of four MS patients has a concomitant medical condition at MS diagnosis, and 5% have two concomitant medical conditions. Although univariate analysis showed that MS patients with comorbidities at diagnosis had higher age, higher baseline disability, higher diagnostic delay , higher relapse rate in the previous year and lower education compared to those without, multivariate analysis demonstrated that older age at diagnosis was the only factor which was significantly associated with comorbidities. The association between previous relapses and comorbidities, that was statistically significant at univariable analysis, disappeared when adjusting for age, thus suggesting that younger age is a confounding factor for a higher relapse activity. Association between age and comorbidities may be explained by the fact that many comorbidities, and particularly cardiovascular disease, metabolic diseases, and cancer, increase their incidence over the life time.

However, and not unexpectedly, the most prevalent concomitant diseases were other autoimmune diseases, and particular thyroid diseases, type 1 diabetes mellitus, and celiac disease. A common genetic background [20] and/or the effect of similar risk factors are thought to contribute to this association. High prevalence of thyroid diseases in MS has been reported before, although it is debated whether it outnumbers the prevalence in the general population[12]. The association between type 1 diabetes and MS has been reported before in the Italian population, particularly from Sardinia and from the North-East[21, 22]. Also celiac disease was reported to be more frequent in MS in a small study[23].

In general, the prevalence of specific comorbidities was lower than previously reported; this is explained, in our opinion, by the fact that we considered comorbidities that were already present at diagnosis, whereas most studies evaluated comorbidities in the MS population, at any time point from diagnosis [5].

Very few ~~data~~ studies, mainly~~mostly~~ ~~from~~ post-marketing~~, studies~~ address the issue of how ~~are available on how~~ comorbidities and treatment choice for MS are associated~~[24, 25]~~ [1]. Neurologists may follow empirical rules while prescribing DMDs in patients with comorbidities, in order to avoid safety issues in patients with more than one disease, or, on the contrary, to affect multiple diseases with one treatment (i.e. fumarate derivatives in patients with MS and psoriasis [26], or natalizumab in patients with MS and Crohn's disease[27]).

One recently published study, where authors analyzed retrospectively administrative and clinical data on 10698 MS patients in Canada, found that specific comorbidities are associated to the likelihood to starting a DMD for MS, with marked difference among provinces, while comorbidities did not influence the choice of treatment [28]. Due to the design of our study, which included patients who started the first DMD upon one year from diagnosis, we did not assess whether comorbidities were associated to increased diagnosis-treatment lag. While we observed a higher percentage of patients with comorbidities among those prescribed with some DMD (GA, dimethylfumarate and teriflunomide), adjusting for age at diagnosis, year of diagnosis, and center showed that such differences were not significant.

Poor tolerance of the first DMD may decrease substantially the quality of life of newly diagnosed patients, as well as expose them to the risk of disease progression due to scarce compliance or to treatment interruption. We found that comorbidities at MS diagnosis are associated to increased rate of switching from the first DMD due to intolerance. Comparing different treatment, IFN-β was associated to high risk of intolerance-switch in presence of comorbidities, whereas patients with comorbidities who were treated with GA did not have an increased risk of switching. Results obtained with natalizumab are explained, by the fact that most cases of intolerance/safety switch from natalizumab in our cohort were due to risk of PML (33/43, 76%). Regarding fingolimod, a very low rate of switch due to intolerance was observed in patients overall. However, this analysis has some limitations: the small size of natalizumab and fingolimod treatment groups makes the confidence intervals for the hazard ratios very wide, precluding the possibility to run pairwise

comparisons among the groups (with appropriate adjustment for multiple testing). Therefore, the results of this analysis generate a hypothesis that calls for further studies to be validated.

Finally, we found that patients with comorbidities had a slightly higher disability at the last follow-up. The difference in the EDSS gain was little, and likely of low clinical importance, but it was significant despite the fact that the analysis was adjusted for many covariates. Since switches due to inefficacy were not affected by comorbidities, we can speculate that inefficacy-switches were mainly driven by acute (inflammatory) events such as relapses or MRI activity, while the long-term EDSS increasing was driven by neurodegenerative processes that appear to be worsened by comorbidities.

In conclusion, the results of this study show that comorbidities at MS diagnosis are frequent and that they are associated to the response to the first treatment, increasing the switch rate due to intolerance, particularly when the first DMD is IFN-β. Due to introduction of oral drugs in 2014 in MS, fewer data were available on the association of comorbidities on safety and efficacy of these drugs. Further studies are warranted to evaluate how newer drugs will perform in MS patients with comorbidities.

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Table 1 Baseline demographic and clinical characteristics of the enrolled cohort

		Overall	Comorbidities	No comorbidities	Univariable p-value*	Mu
Number of patients	n (%)	1877	449 (23.9)	1428 (76.1)		
Age	mean (SD)	35.3 (11.3)	40.1 (11.3)	33.8 (10.9)	< 0.001	
Female %	n (%)	1218 (64.9)	305 (67.9)	913 (63.9)	0.15	
EDSS	mean (SD); median (IQR)	2.1 (1.1); 2.0 (1.5-2.5)	2.2 (1.2); 2.0 (1.5-3.0)	2.0 (1.1); 2.0 (1.0-2.5)	0.001	
Number of patients with EDSS > 3.0	n/tot (%)	268/1865 (14.4)	85/449 (18.9)	183/1416 (12.9)	<0.001	
Time since onset	mean (SD); median (IQR)	3.1 (5.4); 0.8 (0.2-3.4)	3.9 (6.6); 1.1(0.3-3.9)	2.9 (5); 0.8 (0.2-3.1)	0.001	
At least one relapse previous year	n/tot (%)	1590/1858 (85.6)	354/448 (79.0)	1236/1410 (87.7)	< 0.001	
Active lesions	n/tot (%)	736/1603 (45.9)	180/389 (46.3)	556/12144 /(45.8)	0.86	

Spinal cord lesions	n/tot (%)	995/1408 (70.7)	144/347 (70.3)	751/1061 (70.8)	0.69	
> 9 T2 lesions at brain MRI	n/tot (%)	1182/1616 (73.1)	265/394 (67.3)	917/1222 (75.0)	0.62	
Education (number of years)	mean (SD)	11.7 (4.3)	11.2 (4.4)	11.8 (4.3)	0.048	
Follow-up (years)	Median (range)	2.6 (0.02-6.43)	2.57 (0.10-6.43)	2.61 (0.02-6.34)	0.72	
*:Adjusted for center and year of diagnosis						

Revised t**able 2** **Comorbidities categorized by affected system**

Category of comorbidity	**Specific disease**	**N**	% on all patients
Autoimmune	**All**	136	7.2
	Thyroid	85	4.5
	Type 1 diabetes mellitus	16	0.9
	Celiac disease	12	0.6
	Rheumathoid arthritis	6	0.3
	Other	17	0.9
Psychiatric	**All**	99	5.3
	Depression	53	2.8
	Anxiety	17	0.9
	Bipolar disorder	11	0.6
	Psychosis	8	0.4
	Other	10	0.5

Cardiovascular	**All**	96	5.1
	Arterial hypertension	86	4.6
	Cardiac arrhythmias	3	0.2
	Other	7	0.4
Methabolic	**All**	52	2.8
	Hyperlipidemia	34	1.8
	Type 2 diabetes mellitus	12	0.6
	Other	6	0.3
Neurologic	**All**	44	2.3
	Migraine	31	1.7
	Epilepsy	7	0.4
	Other type of Headache	4	0.2
	Other	2	0.1
Gastrointestinal	**All**	23	1.2
Musculoskeletal	**All**	16	0.9
Cancer	**All**	11	0.6

Figure legends

Figure 1 - Proportion of patients with comorbidities according to treatment groups

Figure 2 - Time to tolerance-safety switch according to comorbidity presence at baseline and stratified for first therapy.