Comorbidities affect treatment choice and persistence in RRMS: a multicenter study

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INTRODUCTION AND PURPOSE

- Clinical trials evaluating the efficacy of drugs for multiple sclerosis (MS) usually exclude people with significant comorbidities. This is meant to avoid the exposure of frailer subjects to potentially toxic effects of medications. Due to the lack of data regarding effectiveness and tolerability of drugs in this patient group, they are prescribed treatments based on theoretical and empirical data, according to the clinician's judgement. Therefore, the need for data on the effect of comorbidities on treatment persistence in MS has been recently called for 1, 2. The objective of this study was to assess whether the presence of concomitant diseases affects the choice and the persistence of first treatments for MS.

METHODS

- We retrospectively enrolled patients from 18 MS centers in Italy. 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 criterion was diagnosis since 2010. We collected anonymized demographics and clinical data, name and date of first treatment, date and reason for switch- classified as inefficacy or intolerance (including side effects, pregnancy, patient decision)- and second treatment. Patients without data on presence of comorbidities were excluded from the analysis. We evaluated baseline factors (age, Expanded Disability Status Scale - EDSS-, time between onset and diagnosis, education, presence of active lesions at brain and/or spinal cord MRI) associated with comorbidities by logistic regression. The impact of comorbidities on time to switch during follow-up was assessed by a multivariate Cox model adjusted for baseline characteristics, while the impact of comorbidities on the EDSS change at the last follow-up was evaluated by an analysis of covariance, adjusting for length of follow up, age at diagnosis, baseline EDSS, first treatment, and reason for switch.

RESULTS

- The study population included 1452 patients. Data on comorbidities were available for 1067/1452 patients (73.4%). Mean age at diagnosis was 35.1 years (SD 11.5), females were 705 (66.1%). Year of diagnosis was 2010 (N=266), 2011 (295), 2012 (225), 2013 (132); 2014 (90), 2015 (58). Mean time between disease onset and diagnosis was 2.9 years (SD 4.9; IQR : 0.2-3).
- 266/1067 (24.9%) patients had comorbidity at diagnosis (Figure 1). First treatment included: any type of interferon-beta (IFN) (N=707; 66.3%), glatiramer acetate (GA) (N=172;16.1%), natalizumab (N=65; 6.1%), fingolimod (N=31;2.9%), other treatments (N=45; 4.2%), 4.4% of patients were not treated. Very few patients started dimethyl fumarate or teriflunomide, since these drugs entered the market in 2015 and most patients were enrolled before that date..
- Most common comorbidities were psychiatric (N= 63), internal medicine (N=50), thyroid (N=42), and autoimmune (N=48) diseases; other comorbidities included cephalalgia, infections, hematologic disorders, genetic conditions, cancer, allergy/asthma, and others.
- Patients with comorbidities had higher mean age at diagnosis (39.4 vs 33.7 years, p< 0.001), higher EDSS (median EDSS 2.0 (IQR 1.5-3.0) vs 1.5 (IQR 1.0-2.5), p<0.001)(Figure 2) and lower education (p=0.005). At multivariate analysis, age at diagnosis (OR=1.04; p<0.001) and baseline EDSS (OR=1.13; p=0.053) were retained as independently related to the presence of comorbidities.
- Comorbidities were present in 146/707 (20.7%) patients having IFN as first treatment, 54/172 (31.4%) having GA, 17 (26.2%) under natalizumab and 7/31 (22.6%) under fingolimod (Figure 3, p for heterogeneity = 0.002) (Figure 3) Almost half of treated patients (46.6%) switched therapy after 3 years. Cumulative incidence of treatment switch due to inefficacy at 3 years was 27.7% and of switch due to intolerance 17.2%. Cox regression analysis, adjusted for baseline characteristics at diagnosis (age, EDSS, relapses in the previous year, MRI activity, year of diagnosis) showed that comorbidities did not affect the first treatment switch due to inefficacy, but impacted on the switch due to intolerance (HR 1.48, CI 1.01-2.16, p= 0.046) (Table 1). Patients with comorbidities had a higher risk of switching due to intolerance from IFN as compared to those without comorbidities (HR=2.0; 95% CI: 1.34-3.01), this did not happen for those who were treated with GA (HR=0.39; 95% CI: 0.09-1.76; interaction test, p=0.015; Figure 4).
- EDSS change at last follow up was 0.3 (SD:1.2; IQR: 0-1) for patients with comorbidities and 0.07 (SD:1.1; IQR: -0.5-0.5) for those without (analysis of covariance, adjusted p=0.008) (Figure 5).

DISCLOSURES

Alice Laroni has received personal compensation from Novartis, Genzyme, Biogen and TEVA for public speaking and advisory boards. Alessio Signori received teaching honoraria from Novartis. Giorgia T. Maniscalco received personal compensation from Serono, Biogen and TEVA for public speaking and advisory boards. Roberta Lanzillo received personal compensation from Merck Serono, Novartis, Almirall, Genzyme, and TEVA for public speaking, editorial work and advisory boards. Francesco Saccà received personal compensation from Novartis, Almirall, Genzyme, Forward Pharma and TEVA for public speaking, editorial work and advisory boards. Marinella Clerico received personal compensation for partecipating to advisory boards by Merck Serono and Biogen; travel expenses for congresses paid by Merck, Biogen, Novartis and Genzyme. Salvatore Lo Fermo has received funding for travel and for advisory board from Genzyme, Biogen Idec, Teva, Merck-Serono. Pietro Annovazzi served as advisor and received speaking honoraria from Novartis, Merck Serono, Genzyme, Biogen and Teva Italia. Simona Bonavita received speaker honoraria from Merck Serono, Novartis, Teva and Genzyme; Advisory Board honoraria from Teva, Novartis, Biogen. Damiano Baroncini received honoraria from Almirall for the creation of editorial publications, and travel grants for participation to international congresses from Genzyme and TEVA. Sarah Rasia Nothing to disclose. Cinzia Cordioli received personal compensations for consultant from Merk Serono and Novatis. Luca Prosperini received consulting fees from Biogen and Novartis; speaker honoraria from Biogen, Genzyme, Novartis and Teva; travel grants from Biogen, Genzyme, Novartis and Teva; research grants from the Italian MS Society (Associazione Italiana Sclerosi Multipla) and Genzyme. Eleonora Cocco, Eleonora Cocco received personal compensation from Almirall,Bayer, Biogen, Genzyme, Novartis, Serono and TEVA for public speaking, editorial work and advisory boards.Valentina Torri Clerici received personal compensation from Novartis, Almirall, Genzyme, and Teva for public speaking, editorial work and advisory boards". Arianna Sartori has received funding for travel and/or speaker honoraria from Novartis, Teva, Merck-Serono and Genzyme. Elisabetta Signoriello received personal compensation from Almirall, Biogen, Genzyme, Novartis and Teva for traveling and advisory boards. Annamaria Repice has received personal compensation from Biogen Idec , Genzyme, Novartis and Merck Serono for public speaking and advisory boards. Ignazio Roberto Zarbo has served on scientific advisory board for Biogen Idec, and received funding for travel and/or speaker honoraria from Genzyme, Biogen Idec, Teva, Merck and Novartis. Raffaella Cerqua has received funding for travel and/or speaker honoraria from Genzyme, Biogen Idec, Teva, Merck-Serono and Novartis. Simona Pontecorvo received personal compensation from Almirall, Biogen, Genzyme, and Teva for public speaking and advisory boards.Alessia Di Sapio received personal compensation from Novartis, Biogen, Merck Serono, Teva and Bayer Schering for public speaking and advisory boards; moreover she received funding to partecipate to Congresses and Meetings from Merck Serono, Biogen, Novartis, Genzyme, Allergan and Medtronic.Luigi Lavorgna has received funding for travel and/or speaker honoraria from Novartis, Genzyme, Teva, Merck, Almirall and Bayer. Caterina Barrilà: nothing to disclose.Sara La Gioia Nothing to disclose.Barbara Frigeni Nothing to disclose.Pietro Iaffaldano has served on scientific advisory boards for Biogen Idec, Bayer and Genzyme and has received funding for travel and/or speaker honoraria from Genzyme, Biogen Idec, Teva, Merck-Serono and Novartis. Eleonora Binello does not have disclosures.Cinzia Valeria Russo does not have disclosures.Sabrina Esposito does not have disclosures.Jessica Frau serves on scientific advisory boards for Biogen, received honoraria for speaking from Merck Serono, Biogen and Teva and received research grant from Serono.Silvia Rossi Dr. Rossi acted as an Advisory Board member of Biogen Idec, Bayer Schering, Merck Serono, Teva, Novartis and Genzyme, and received funding for traveling and honoraria for speaking or writing from Biogen Idec, Merck Serono, Teva, Novartis, Bayer Schering, Genzyme, Almirall. She received support for research project by Teva, Merck Serono and Bayer Schering and is involved as principal investigator in clinical trials for Teva and Roche. Fabio Gallo received teaching fees from Novartis.Maria Pia Sormani has received personal compensation for consulting services and for speaking activities from Merck Serono, Teva, Novartis, Roche, Genzyme and Biogen; Novartis Pharma supported the meetings of the MUST group but was not involved in this project nor did it have any access to the data.

Figure 1

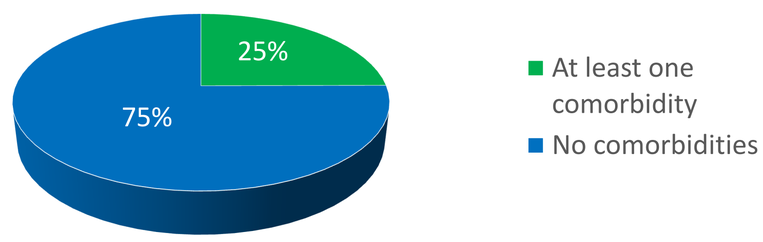


Figure 2

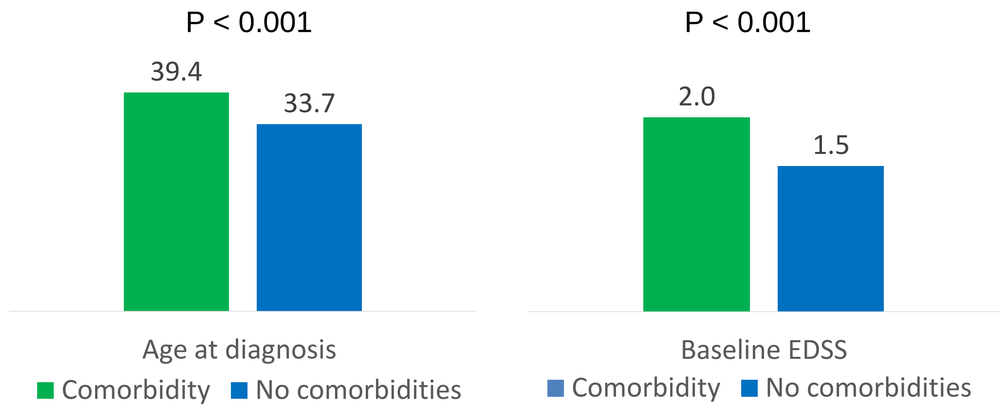


Figure 3

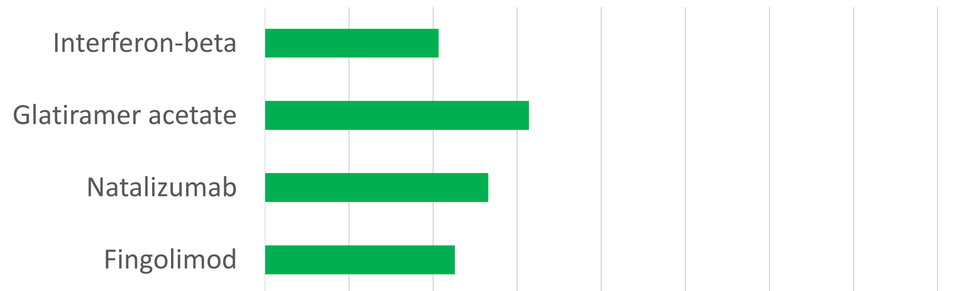


Figure 4

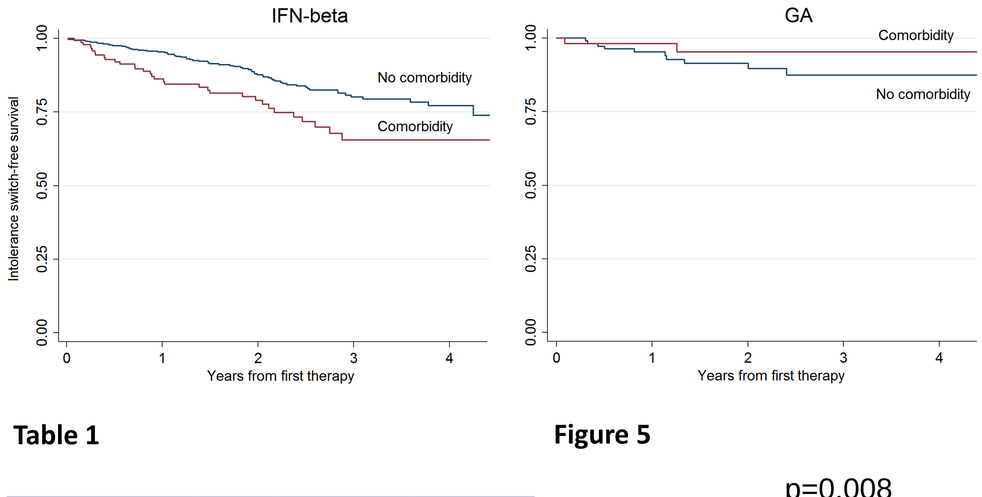
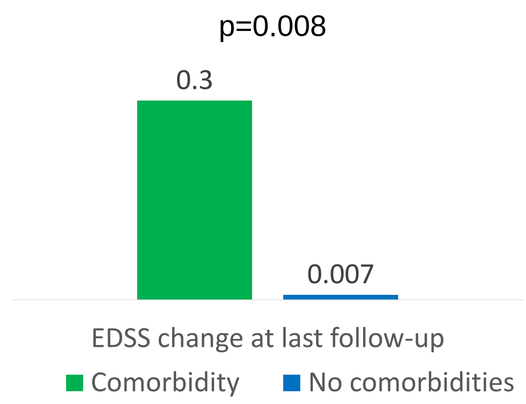


Table 1

Variable	HR	CI (95%)	P value
Year of diagnosis	1.30	1.10, 1.54	0.002
Comorbidities	**1.48**	**1.01, 2.16**	**0.046**
FTY/NAT vs INF/GA	2.11	1.36, 3.27	0.001
Baseline EDSS	1.21	1.04, 1.41	0.016
Years from onset	0.953	0.91, 0.99	0.030

Figure 5



CONCLUSION

In conclusion, the presence of comorbidities at disease diagnosis of MS affects about one every four patients and is associated with higher age at diagnosis and higher risk of disability worsening over time. The presence of comorbidities affects the first treatment choice and increases the likelihood to switch from first treatment due to intolerance, with a significant impact on persistence of treatment, especially for those treated with IFN as first therapy. It will be of interest to study how newer drugs will change this scenario.

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