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

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Introduction

There are different disease modifying drugs (DMDs) licensed for relapsing multiple sclerosis (RRMS), making it difficult for neurologists to choose among treatments at disease onset.

Objectives

- To evaluate the change in therapeutic approach with the availability of new first-line oral drugs, teriflunomide and dimethylfumarate (Oral) in Italy.
- To compare the clinical efficacy of the different first line choices in treatment naïve RRMS patients.

Methods

Two cohorts of naïve RRMS patients receiving the first DMD from 18 Italian MS centers have been extracted in 2016 from the Italian MS Register.

- 1st cohort: first DMD prescription during the 2 years prior to the marketing of Teriflunomide in Italy (***Old Era***).
- 2nd cohort: first DMD prescription during the 12 months after the marketing of Dimethylfumarate in Italy (***New Era***).

- Predictors of treatment choice have been evaluated by regression models with an unstructured correlation-type matrix to account for the hierarchical nature of the data (patients clustered within geographic area (north, center and south)).
- The intra-class correlation coefficient (ICC) was calculated to assess the variation in the use of treatment choice among geographic area; a greater impact of the geographic area is shown by higher ICC values.
- The relapse risk during the course of the first DMD prescribed in the ***New Era*** cohort stratified by the baseline EDSS score (≤3, >3) has been evaluated using a Poisson regression model.

Results

Baseline characteristics stratified by the first treatment choice – IFNB or GA – of the 1st cohort of RRMS patients (n=1,795) are reported in. The presence or not of comorbidities, the age at the time of the first DMD prescription and the disease duration were all factors associated to the first treatment choice in the ***Old Era*** (**table 2**). Variation in the use of treatment choice among geographic area as impact of ICC was comprised between 2% and 20%. IFNB was more frequently prescribed as first-line agent in the south of Italy. **Table 1**

Table 1. Cohort 1 – Baseline characteristics stratified by first treatment choice – IFNB or GA

VARIABLE	IFNB	GA	P - VALUE
N. Group	1373	422	
Age at the first DMD prescription, years, Median (IQR)	34.25 (26.85-43.50)	40.40 (32.00-48.10)	**<.0001**
Female, n (%)	939 (68.39)	303 (71.80)	0.18
Presence of Comorbidity, n (%)	182 (13.26)	83 (19.67)	**0.001**
Disease duration at the first DMD prescription, months, Median (IQR)	21.90 (6.90-72.70)	39.65 (12.90-127.50)	**<.0001**
EDSS at the first DMD prescription, Median (IQR)	2.00 (1.00-3.00)	2.00 (1.50-3.50)	**0.02**
Number of Relapses Before Treatment Start, Median (IQR)	2.00 (1.00-3.00)	2.00 (1.00-3.00)	**0.05**
Oligoclonal banding status, n (%)			
Negative	89 (6.48)	22 (5.21)	0.38
Positive	573 (41.73)	167 (39.57)	
Onset symptom, n (%)			
Isolated Optic Neuritis	334 (24.33)	96 (22.75)	0.59
Isolated Brain-Stem Syndrome	278 (20.25)	86 (20.38)	
Isolated Spinal Syndrome	327 (23.82)	90 (21.33)	
Isolated Supratentorial Syndrome	287 (20.90)	101 (23.93)	
Multifocal	147 (10.71)	49 (11.61)	

Table 2. Predictors of First Treatment Choice during the *Old Era*

Multilevel (AREA) (n=1788)	GA		IFNB 1a IM		IFNB 1b		IFNB 1a 22 mcg SC		IFNB 1a 44 mcg SC	
Predictor	**OR (95% CI)**	**p**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**p**
Female sex	0.91 (0.67-1.24)	0.56	1.21 (0.93-1.56)	0.16	0.91 (0.67-1.24)	0.56	1.2 (0.90-1.61)	0.21	**0.74 (0.58-0.93)**	**0.01**
Onset symptom (Isolated Optic Neuritis as reference category)										
Multifocal	0.97 (0.59-1.59)	0.90	0.8 (0.52-1.24)	0.32	0.97 (0.59-1.59)	0.90	0.92 (0.57-1.47)	0.72	1.02 (0.67-1.55)	0.92
Isolated Supratentorial Syndrome	0.71 (0.46-1.10)	0.12	0.89 (0.63-1.25)	0.50	0.71 (0.46-1.10)	0.12	1.01 (0.70-1.47)	0.95	1.03 (0.73-1.44)	0.89
Isolated Spinal Syndrome	0.92 (0.61-1.40)	0.71	0.88 (0.62-1.23)	0.45	0.92 (0.61-1.40)	0.71	0.83 (0.56-1.22)	0.35	1.37 (1.00-1.89)	**0.05**
Isolated Brain-Stem Syndrome	0.8 (0.52-1.24)	0.32	1.07 (0.76-1.50)	0.71	0.8 (0.52-1.24)	0.33	0.78 (0.52-1.16)	0.22	1.17 (0.84-1.64)	0.35
Positive Oligoclonal banding status	1.18 (0.56-2.45)	0.67	**0.58 (0.37-0.92)**	**0.02**	1.18 (0.56-2.45)	0.67	0.65 (0.40-1.06)	0.09	**2.51 (1.46-4.30)**	**0.0008**
Presence of Comorbidity	**0.61 (0.38-0.97)**	**0.04**	1.14 (0.82-1.59)	0.44	**0.61 (0.38-0.97)**	**0.04**	1 (0.68-1.45)	0.98	0.73 (0.52-1.03)	0.08
Age at the first DMD prescription	**1.02 (1.00-1.03)**	**0.03**	1.01 (1.00-1.02)	0.21	**1.02 (1.00-1.03)**	**0.03**	**0.97 (0.95-0.98)**	**<.0001**	**0.98 (0.97-0.99)**	**0.0009**
Disease duration at the first DMD prescription	1 (1.00-1.00)	0.59	**1 (1.00-1.00)**	**0.01**	1 (1.00-1.00)	0.59	1 (1.00-1.00)	0.12	**1 (0.99-1.00)**	**<.0001**
EDSS at the first DMD prescription	**1.24 (1.12-1.36)**	**<.0001**	**0.82 (0.75-0.90)**	**<.0001**	**1.24 (1.12-1.36)**	**<.0001**	0.97 (0.88-1.07)	0.52	1.01 (0.93-1.10)	0.85
Number of Relapses Before Treatment Start	1.03 (0.93-1.14)	0.58	0.85 (0.76-0.94)	0.002	1.03 (0.93-1.14)	0.58	1.08 (0.97-1.19)	0.16	**1.15 (1.05-1.25)**	**0.002**

Results

Baseline characteristics stratified by the first treatment choice – injectables or oral – of the 2nd cohort of RRMS patients (n= 1,097) are reported in **Table 3.** No significant predictors were associated to the dimethylfumarate choice. Teriflunomide was more significantly prescribed in patients with low rates of comorbidities, who were older and with a longer disease duration than patients who received the injectables or the dymethylfumarate treatment (**table 4**). Variation in the use of oral treatment choice among geographic area as impact of ICC was 7%.

The relapse risk during the course of the first DMD prescribed in the ***New Era*** cohort was evaluated in two separated models based on the baseline EDSS score. In patients with a baseline EDSS > 3 a higher relapse risk was found in younger patients (**Table 5**).

In patients with a baseline EDSS ≤ 3 increasing age and disease duration at the treatment start, and choice of dimethylfumarate were associated to a lower risk of relapses, whereas a higher number of relapse before the first DMD prescription and the choice of teriflunomide as first DMD were associated to an increased risk of relapses (**table 5**).

Table 3. Cohort 2 *New Era* – Baseline characteristics stratified by first treatment choice – Oral agents or Injectables

VARIABLE	Oral	Injectables	P
N. Group	338	759	
Age at the first DMD prescription, years, Median (IQR)	**42.10 (33.20-49.90)**	**35.30 (26.80-44.30)**	**<.0001**
Female, n (%)	233 (68.93)	503 (66.27)	0.39
Presence of Comorbidity, n (%)	**22 (6.51)**	**86 (11.33)**	**0.01**
Disease duration at the first DMD prescription, months, Median (IQR)	**47.25 (10.90-154.20)**	**18.05 (6.90-57.30)**	**<.0001**
EDSS at the first DMD prescription, Median (IQR)	**2.00 (1.00-3.00)**	**1.50 (1.00-2.50)**	**<.0001**
Number of Relapses Before Treatment Start, Median (IQR)	2.00 (1.00-3.00)	2.00 (1.00-3.00)	0.85
Oligoclonal banding status, n (%)			
Negative	**18 (5.33)**	**48 (6.32)**	**<.0001**
Positive	**92 (27.22)**	**328 (43.21)**	
Onset symptom, n (%)			
Isolated Optic Neuritis	**68 (20.12)**	**162 (21.34)**	**0.05**
Isolated Brain-Stem Syndrome	**75 (22.19)**	**170 (22.40)**	
Isolated Spinal Syndrome	**59 (17.46)**	**182 (23.98)**	
Isolated Supratentorial Syndrome	**97 (28.70)**	**165 (21.74)**	
Multifocal	**39 (11.54)**	**80 (10.54)**	
Geographical Area, n (% by row)			
North	**46 (28.22)**	**117 (71.78)**	**<.0001**
Center	**80 (49.69)**	**81 (49.31)**	
South	**212 (27.43)**	**561 (72.57)**	

Table 4. Predictors of First Treatment Choice in the *New Era*

Multilevel (AREA) (n=1097)	Dimethylfumarate		Teriflunomide	
Predictor	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Female sex	1.18 (0.83-1.69)	0.36	0.88 (0.57-1.36)	0.57
Onset symptom (Isolated Optic Neuritis as reference category)				
Multifocal	0.82 (0.46-1.48)	0.51	1.24 (0.55-2.80)	0.61
Isolated Supratentorial Syndrome	0.92 (0.57-1.46)	0.71	1.57 (0.82-3.04)	0.18
Isolated Spinal Syndrome	0.65 (0.39-1.10)	0.11	1.6 (0.80-3.20)	0.18
Isolated Brain-Stem Syndrome	0.7 (0.42-1.15)	0.16	**2.01 (1.04-3.89)**	**0.04**
Positive Oligoclonal banding status	0.82 (0.40-1.68)	0.59	0.87 (0.31-2.43)	0.79
Presence of Comorbidity	0.67 (0.36-1.24)	0.20	**0.43 (0.19-0.96)**	**0.04**
Age at the first DMD prescription	1 (0.98-1.02)	0.89	**1.07 (1.05-1.09)**	**<.0001**
Disease duration at the first DMD prescription	1 (1.00-1.00)	0.21	**1 (1.00-1.01)**	**0.0006**
EDSS at the first DMD prescription	1.08 (0.96-1.22)	0.20	1.12 (0.97-1.28)	0.12
Number of Relapses Before Treatment Start	1.04 (0.91-1.18)	0.60	0.9 (0.78-1.04)	0.16

Table 5. Effectiveness of the First DMD in the 2nd cohort stratified by the baseline EDSS score – Number of Relapses – Poisson Regression Model

	EDSS ≤ 3		EDSS > 3	
Variable	**IRR (95% CI)**	**p**	**IRR (95% CI)**	**p**
Female sex	0.96 (0.72-1.28)	0.80	1.48 (0.75-2.94)	0.26
Age at the first DMD prescription	**0.95 (0.94-0.97)**	**<.0001**	**0.95 (0.93-0.98)**	**0.0006**
Onset symptom (Isolated Optic Neuritis as reference category)				
Multifocal	0.94 (0.56-1.59)	0.83	0.15 (0.02-1.18)	0.07
Isolated Supratentorial Syndrome	0.67 (0.40-1.14)	0.14	0.96 (0.32-2.91)	0.94
Isolated Spinal Syndrome	1.17 (0.71-1.92)	0.55	1.61 (0.63-4.08)	0.32
Isolated Brain-Stem Syndrome	0.96 (0.56-1.65)	0.89	1.90 (0.81-4.47)	0.14
Positive Oligoclonal banding status	1.80 (0.93-3.47)	0.08	0.67 (0.18-2.54)	0.56
Presence of Comorbidity	1.21 (0.77-1.90)	0.40	0.88 (0.25-3.03)	0.84
Disease duration at the first DMD prescription	**0.98 (0.96-1.00)**	**0.03**	1.00 (0.98-1.02)	0.91
Number of Relapses Before Treatment Start	**1.32 (1.18-1.47)**	**<.0001**	1.02 (0.84-1.25)	0.82
Treatment				
Teriflunomide	**1.95 (1.03-3.69)**	**0.04**	1.04 (0.27-3.98)	0.95
Injectables	1.17 (0.74-1.84)	0.51	1.70 (0.62-4.62)	0.30
Dimethylfumarate	1.00	.	1.00	.

Conclusions

Our results indicate that in Italy GA was used more frequently in patients older and with more comorbidity than patients treated with IFNB before the introduction of oral first-line DMD.

After the introduction of the new first line oral DMDs, these drugs have been more frequently used in patients without comorbidity in comparison to injectable DMDs. This latter finding was more pronounced in patients treated with teriflunomide. In patients less disabled (EDSS ≤3) the use of dimethylfumarate was associated to a reduced risk of relapses.

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