ORAL AGENTS IN MULTIPLE SCLEROSIS IN A REAL-LIFE SETTING.

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OBJECTIVES

The availability of oral medications besides the classical injectables for the treatment of relapsing-remitting Multiple Sclerosis (MS) has represented a revolution for both patients and clinicians, since they allowed to overcome many problems related to site-injection reactions and low compliance and they were hypothesized to guarantee an increase in terms quality of life.
The aim of our retrospective single-center study was to analyze the tolerability and safety of oral treatments in a real-life setting.

MATERIALS and METHODS

We collected the clinical and paraclinical data of consecutive MS patients of our MS Centre who have been treated with oral medications. In particular, we considered the frequency and severity of adverse events occurred during treatment, comparing the three oral agents currently available (fingolimod, teriflunomide, and dimethyl fumarate). Statistical analyses were performed using SPSS 22.0 for Windows. Chi-square test and independent-samples Kruskal-Wallis test and have been applied, as appropriate.

RESULTS

63 MS patients have been treated with oral medications (25,6% fingolimod, 23,1% teriflunomide, 32,1% dimethyl fumarate). Clinical characteristics of patients are shown in table 1 (data are updated to 6th June 2016). There was no difference between groups in terms of gender distribution (p=0,15). Age at disease onset was higher in teriflunomide treated patients (mean±SD: fingolimod 25,3±8,1, teriflunomide 33,5±10,2, dimethyl fumarate 29,7±8,6, p=0,030), as well as age at treatment onset (mean±SD: fingolimod 39,2±6,5, teriflunomide 46,1±10,0 dimethyl fumarate 40,3±10,6, p=0,024). As expected, there was a higher percentage of patients switching from a previous treatment in the fingolimod group (90% vs 66,7% and 56,0% in teriflunomide and dimethyl fumarate groups, respectively; p=0,045), in particular from natalizumab (83,3%). Moreover, patients on dimethyl fumarate had a lower EDSS at the beginning of treatment (median EDSS 2,5, 1,5, and 1 for fingolimod, teriflunomide, and dimethyl fumarate, respectively; p= 0,002).
Overall number of adverse events was not significantly different in fingolimod group compared to teriflunomide (25,0% vs 44,4%, p=0,21), while was significantly lower in fingolimod group compared to dimethyl fumarate group (25,0% vs 60,0%, p=0,019); this observation was not confirmed in a multivariate analysis. We did not observe any severe adverse event. Adverse events leading to discontinuation were similar in all groups (20,0%, 37,5%, and 26,7% in fingolimod, teriflunomide, and dimethyl fumarate group respectively, p=0,77). Discontinuation rates were 5%, 22,2%, and 16,0% in fingolimod, teriflunomide, and dimethyl fumarate group respectively (p=0,302), with the following percentages of discontinuation due to adverse events: 5,0%, 11,1%,and 16,0% (p=0,506).
In a multivariate analysis model, the only variable remaining significantly different between groups was treatment duration.

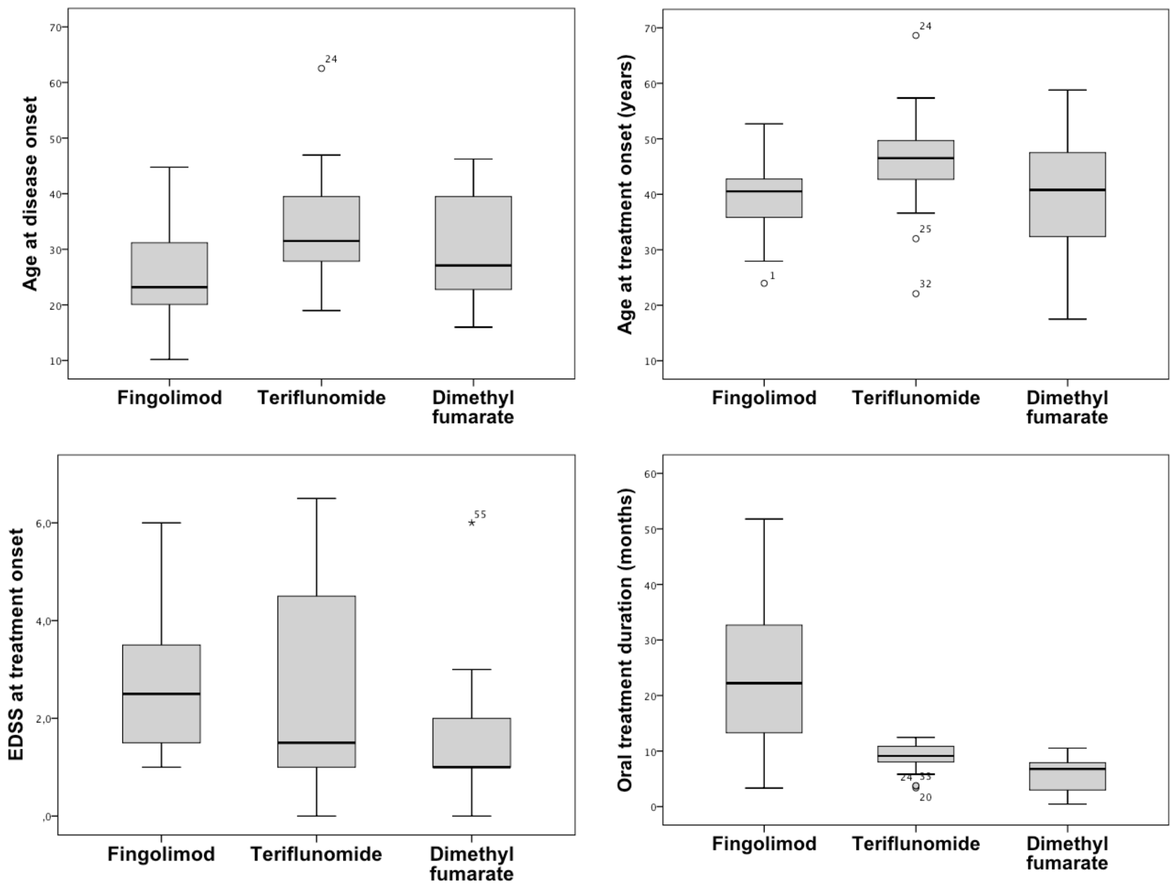

Figure 1. Clinical characteristics of patients. Box plot of age at disease onset, age at treatment onset, EDSS at treatment onset and oral treatment duration of patients on different oral treatment (fingolimod, teriflunomide and dimethyl fumarate). The upper line of the box marks the75th percentile, the middle line is the median value and the lower line specifies the 25th percentile. Whiskers above and below the box indicate the 90th and 10th percentiles, respectively. Dots indicate the outlier values within each group.

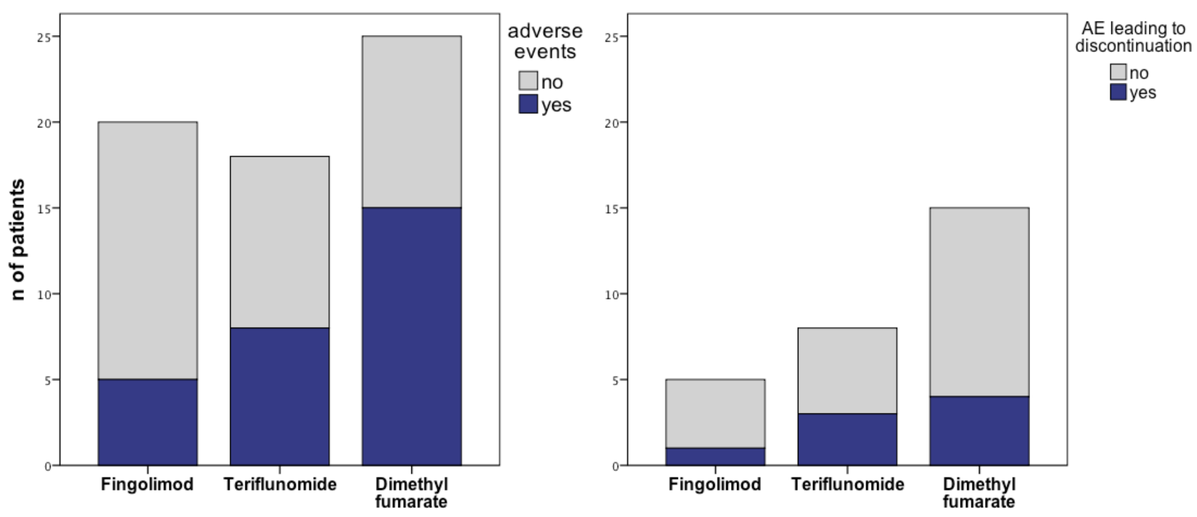

Figure 2. Adverse events. The bar charts show the number of patients presenting adverse events within each treatment group (fingolimod, teriflunomide and dimethyl fumarate).

Characteristics of patients	Fingolimod	Teriflunomide	DMF	Fingolimod vs teriflunomide (p)	Fingolimod vs DMF (p)	Teriflunomide vs DMF (p)	p*
N patients	20 (25,6)	18 (23,1)	25 (32,1)				
Gender							
M	3 (15,0%)	7 (38,9%)	10 (40,0%)	0,095	0,066	0,941	0,150
F	17 (85,0%)	11 (61,1%)	15 (60,0%)				
Age at MS onset	25,3 ± 8,1	33,5 ± 10,2	29,7 ± 8,6	0,011	0,100	0,200	0,030
Age at treatment onset	39,2 ± 6,5	46,1 ± 10,0	40,3 ± 10,6	0,003	0,802	0,065	0,024
Switch from previous treatment	18 (90,0%)	12 (66,7%)	14 (56,0%)	0,078	0,012	0,480	0,045
Previous treatment duration (m)	29,0 ± 26,8	51,6 ± 57,4	87,9 ± 72,4	0,083	0,016	0,211	0,028
Reasons for switch							
Switch for inefficacy	2 (11,1%)	3 (25,0%)	5 (35,7%)	0,317	0,095	0,555	0,251
Switch for side effects	1 (5,6%)	8 (66,7%)	8 (57,1%)	<0,001	0,001	0,619	0,001
Switch for JCV	14 (77,8%)	0 (0%)	1 (7,1%)	<0,001	<0,001	0,345	<0,001
Baseline EDSS	2,7 ± 1,3	2,4 ± 2,2	1,34 ± 1,26	0,164	<0,001	0,164	0,002
Treatment duration	24,6 ± 14,6	8,85 ± 2,9	5,8 ± 3,1	<0,001	<0,001	0,002	<0,001
Adverse events (AE)	5 (25,0%)	8 (44,4%)	15 (60,0%)	0,207	0,019	0,313	0,064
AE leading to discontinuation	1 (20,0%)	3 (37,5%)	4 (26,7%)	0,506	0,776	0,591	0,771
Discontinuation for any reason	1 (5,0%)	4 (22,2%)	4 (16,0%)	0,117	0,243	0,605	0,302
Time to discontinuation	18,0 ± 0	7,9 ± 2,7	3,5 ± 2,6	0,480	0,157	0,050	0,061
Discontinuation for AE	1 (100%)	3 (60%)	4 (100%)	0,439	na	0,151	0,287
Discontinuation for AE (global)	1 (5,0%)	3 (11,1%)	4 (16,0%)				0,506
Discontinuation for inefficacy	0 (0%)	1 (20%)	0 (0%)	0,624	na	0,343	0,574
EDSS end of treatment	2	2,6 ± 1,7	2 ± 2	1,000	1,000	0,763	0,074
Relapses during treatment	4 (20,0%)	3 (16,7%)	0 (0,0%)	0,791	0,019	0,034	0,964

Table 1. Clinical characteristics of patients. Mean ± standard deviation or median (range; * Chi-square test or Kruskal-Wallis test, where appropriate. EDSS: Expanded Disability Status Scale; DMF: dimethyl fumarate; AE: adverse events; na: not available; ns: not significant.

DISCUSSION and CONCLUSIONS

Our study, despite the limitations related to the small number of patients, the short follow-up, and the differences in terms of baseline characteristics between groups, confirms the well-known safety data of the literature. Oral medications for MS were well tolerated; side effects were generally mild and led to discontinuation in a low percentage of patients. The differences in terms of adverse events between the medications observed in the univariate analysis were not confirmed in a multivariate model, possibly due to the small sample size.

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DISCLOSURES

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