Efficacy & Tolerability of Oral versus Injectable Disease Modifying Therapies in Multiple Sclerosis

Erin E. Longbrake, MD, Ph.D.[1] Anne H. Cross, MD[1] & Amber Salter, Ph.D.[2]

[1]Department of Neurology, Washington University in St. Louis [2]Division of Biostatistics, Washington University in St. Louis

Abstract

Importance: The advent of oral disease modifying therapies (DMTs) fundamentally changed the treatment of multiple sclerosis (MS). Nevertheless, impressions of their relative efficacy and tolerability are primarily founded on expert opinion. Comparative data are needed.

Objective: To determine whether oral DMTs were better tolerated and/or more effective for controlling MS compared to injectable therapies (INJ) in clinical practice.

Design/Setting: Retrospective cohort study at a single comprehensive MS center.

Participants: 481 patients with relapsing multiple sclerosis were sequentially enrolled between March 2013 and March 2015. Follow up data were collected for an additional 6 months after enrollment ended.

Exposures: Patients were enrolled upon initiation of a new oral (fingolimod [FGD], teriflunomide [TER], or dimethyl fumarate [DMF]) or INJ therapy for MS. Both treatment-naïve patients and those switching to a new DMT were included.

Main Outcomes: Outcomes included on-drug MS activity (defined as a clinical MS relapse or new MRI activity during treatment) and DMT discontinuation.

Results: Cox proportional hazards models were used to control for baseline differences among patients initiating oral versus injectable DMT. Subsequently, sensitivity analyses using propensity-weighted matching were performed. A higher proportion of TER-treated patients experienced MS activity compared to those treated with INJ (p=0.0054) in the adjusted model. Breakthrough MS was equally prevalent among FGD and DMF-treated compared to INJ-treated patients. Sensitivity analyses using propensity matching to compare each oral DMT to INJ confirmed these findings. Overall, 32-46% of patients initiating DMT discontinued or switched treatments during the study. After controlling for baseline differences, discontinuation rates were comparable across treatment groups.

Conclusions & Relevance: In this cohort, oral and injectable DMTs were equally well tolerated, but TER appeared less effective for controlling MS activity than INJ DMTs. These findings will help inform the selection of the most appropriate DMT for MS patients, but should be validated in an independent patient cohort.

Methods

Chart reviews: Demographic and clinical data were extracted from the medical record including: age, sex, race, time since diagnosis, number of previous DMTs, estimated disability status score (EDSS), relapses within the last 12 months (0 vs ≥1) and prescribing neurologist. EDSSs were categorized into mild (EDSS 0-3), moderate (EDSS 3.5-5.5), or severe disability (EDSS ≥6). Outcomes were: on-treatment MS activity (including both clinical relapses and new MRI disease), treatment discontinuation, and reasons for discontinuation.

Statistical Analysis: Demographic and clinical characteristics were summarized using descriptive statistics. Only the first observation for each patient was used for baseline comparisons. A Cox proportional hazards model accounting for recurrent events was used to evaluate the time to discontinuation and MS disease activity to control for differences in baseline covariates.

Sensitivity Analysis: Propensity score matching was used to evaluate the robustness of the adjusted model results in a sample which is more homogeneous at baseline. Propensity scores were estimated using 3 separate logistic regression models with FGD/INJ, TER/INJ and DMF/INJ as the dependent variable and age, sex, race, prescribing physician, disease duration, categorized EDSS, presence of relapses in last 12 months, number of prior DMTs and length of follow-up as potential confounders. Patients initiating FGD, TER, or DMF were propensity-score matched to patients initiating INJ. The matching process used the nearest neighbor method within specified caliper widths (caliper = 0.20*standard deviation [logit of the Propensity Score]) without replacement. The absolute standardized differences of the covariates for the unmatched and matched cohorts were compared between the groups. After propensity matching, time to event outcomes between matched groups were tested using Cox proportional hazards model with robust standard errors to account for the within-pair homogeneity in matched sample model.

Acknowledgements

No specific funding was received for this study. Dr. Longbrake is a Sylvia Lawry Fellow of the National MS Society.
Dr. Cross was supported by the Manny & Rosalyn Rosenthal – Dr. John L. Trotter Chair in Neuroimmunology from the Foundation for Barnes Jewish Hospital
The authors would like to acknowledge Dr. Gregory Wu for his contributions to this work

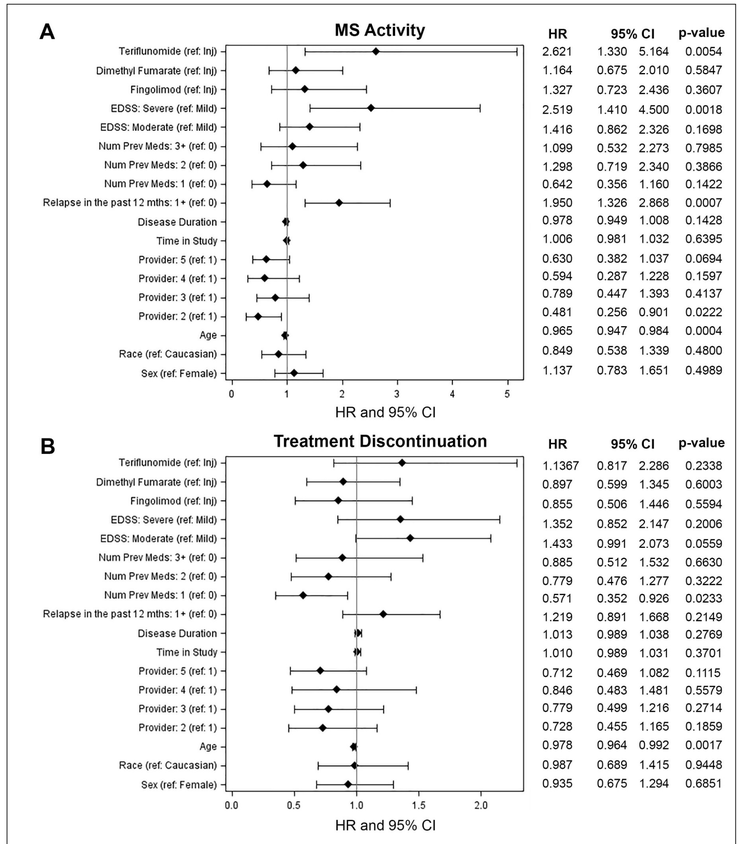

Figure 1: Forest plots of hazard ratios (HR) for MS activity (A) and treatment discontinuation (B) after controlling for baseline variables. CI: confidence interval.

Conclusions

- After controlling for baseline differences, patients initiating teriflunomide were significantly more likely to experience on-drug MS activity compared to patients initiating injectable disease modifying therapy
- Patients were equally likely to discontinue oral and injectable DMTs
- Further study of the comparative effectiveness of MS DMTs is needed

	INJ (n=150)	DMF (n=254)	TER (n=83)	FGD (n=92)	p-value
Females, n (%)	118 (78.7)	183 (72.0)	68 (81.9)	67 (72.8)	0.107
Age, mean (SD)	41.6 (13.1)	44.7 (12.2)	49.4 (10.4)	39.8 (9.3)	<0.001
Caucasian, n (%)	120 (80.0)	216 (85.0)	70 (84.3)	71 (77.2)	0.020
MS duration, years, mean (SD)	5.4 (8.2)	10.6 (9.4)	12.2 (9.8)	7.1 (6.9)	<0.001
Follow-up duration, months, mean (SD)	18.2 (7.7)	20.4 (6.5)	20.3 (7.2)	17.2 (7.2)	0.013
Number of previous meds, n (%)					
0	77 (51.3)	33 (13.0)	4 (4.8)	11 (12.0)	<0.001
1	34 (22.7)	75 (30.0)	41 (49.4)	34 (37.0)	
2	24 (16.7)	73 (28.7)	22 (26.5)	25 (27.2)	
3+	15 (10.0)	73 (28.7)	16 (19.3)	22 (23.9)	
Physician, n (%)					
1	27 (18.0)	24 (9.5)	6 (7.2)	14 (15.2)	<0.001
2	38 (25.3)	58 (22.8)	17 (20.5)	7 (7.6)	
3	19 (12.7)	33 (13.0)	38 (45.8)	33 (26.8)	
4	19 (12.7)	23 (9.1)	3 (3.6)	7 (7.6)	
5	47 (31.3)	116 (45.7)	31 (33.7)	31 (33.7)	
Disability					
Mild (EDSS 0-3)	110 (73.3)	143 (56.3)	43 (51.8)	52 (56.5)	<0.001
Moderate (EDSS 3.5-5.5)	29 (19.3)	46 (18.11)	19 (22.9)	30 (32.6)	
Severe (EDSS ≥6.0)	11 (7.3)	65 (25.6)	21 (25.3)	10 (10.9)	
Relapses in last 12 months, n (%)	92 (61.3)	112 (44.1)	27 (32.5)	46 (50.0)	<0.001
On-drug MS activity, n (%)	29 (19.3)	54 (21.3)	25 (30.1)	24 (26.1)	0.167
Discontinued DMT, n (%)	58 (38.7)	91 (35.8)	38 (45.8)	30 (32.6)	0.178
Switched to a different DMT	46 (79.3)	75 (82.4)	31 (81.6)	24 (80.0)	
Permanently discontinued	12 (20.7)	15 (16.5)	6 (15.8)	6 (20.0)	
Censored	0	1 (1.1)	1 (2.6)	0	

Table 1: Descriptive Data for the Cohort

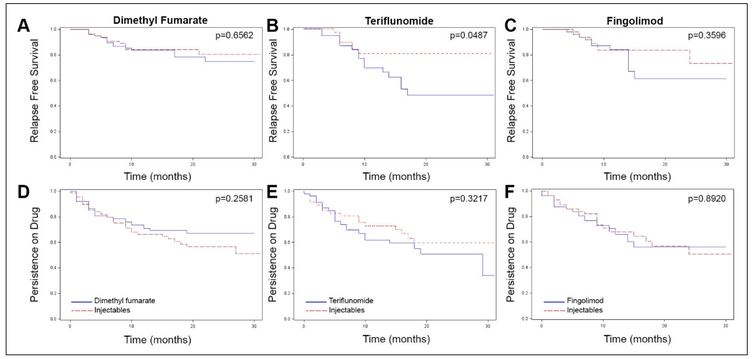

Figure 2: MS activity and persistence on therapy for oral (blue) versus injectable (red) disease modifying therapies after propensity matching.
After propensity weighted matching, 88 DMF-treated patients, 46 TER-treated patients and 56 FGD-treated patients were matched with comparable INJ-treated patients. On-drug MS activity (A-C) and persistence on drug (D-F) were evaluated. Kaplan Meier time to event analyses are shown.