Predictors of Switching First-Line Disease-Modifying Therapy for MS Patients

Barbara Teter,[1,2] Neetu Agashivala,[3] Katelyn S. Kavak,[1] Lynn Chouhfeh,[1] Ron Hashmonay,[3] Bianca Weinstock-Guttman,[1,2] on behalf of the Investigators of the New York State Multiple Sclerosis Consortium

[1]Department of Neurology, Jacobs Neurological Institute, State University of New York at Buffalo, Buffalo, NY; [2]New York State Multiple Sclerosis Consortium, Buffalo, NY; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ

University at Buffalo
The State University of New York

DISCUSSION AND CONCLUSIONS

► MRI activity, EDSS progression, and ≥2 relapses were the most significant predictors of a therapy switch decision in patients with suboptimal response to first-line DMT.
  – MRI activity was 6.3 times as likely to be linked to a therapy switch decision compared with 1 relapse.
► Patients who had experienced combinations of MS events (1 relapse plus EDSS worsening or 1 relapse plus EDSS worsening plus MRI worsening) tended to be stable on their initial DMT for longer periods of time before their first MS event and were less likely to switch therapy.

► Patients who are older at DMT initiation may give less consideration to changing therapy.
► Further study in the nonswitch group may be able to predict switching through analysis of second MS events.
► The likelihood and drivers of therapy switch may change with expanding therapy options; at the time of this study (1996–2009), few therapy options (β interferons, glatiramer acetate, and natalizumab) were available

INTRODUCTION

► In clinical trials, a significant proportion of patients with MS experience breakthrough relapses or disability worsening while under treatment with first-line disease-modifying therapies (DMTs).[1-4]
► Switching DMTs is a common strategy for suboptimal responders, and studies have shown that switching therapy can improve outcomes.[5-12]
► There are no definitive criteria to guide therapy switch decisions, and factors governing these decisions in real-world clinical practice are not well documented.
► The New York State Multiple Sclerosis Consortium (NYSMSC) longitudinal registry of MS care center patients provides data on clinical history and treatment history in real-world clinical practice rather than in the controlled environment of randomized trials.[13]
  – The NYSMSC registry is representative of the general MS population.
► The objective of this retrospective study was to identify clinical and demographic characteristics that predict therapy switching in patients with relapsing-remitting MS (RRMS) following suboptimal response to first-line therapy.

METHODS

Study Design and Patients

► This was a retrospective study of longitudinal registry data from the NYSMSC, which comprises 14 MS centers or neurology practices across New York State.
► The registry captures demographic, clinical, and patient-reported data at registration and consecutive annual clinical follow-up visits.
► Data were analyzed for patients enrolled in the NYSMSC registry from 1996–2009; 9 MS treatment centers participated in chart review follow-up.
  – Inclusion criteria were RRMS with ≥3 years of follow-up and interferon β or glatiramer acetate as initial DMT.
► Suboptimal response to first-line DMT was defined as a clinically determined MS event: (1) relapse; (2) Expanded Disability Status Scale (EDSS) worsening (increase of ≥1.0 for EDSS ≤5.5 or ≥0.5 for EDSS ≥6.0); (3) magnetic resonance imaging (MRI) worsening recorded as MRI worsening, new T2 lesions, new gadolinium-enhancing lesions, or new black holes; or (4) a combination of 1–3.
► Switchers were defined as those who discontinued their initial DMT and started another DMT within 6–12 months following the first MS event that was experienced while on the initial DMT.
  – Discontinuation of add-on medication (azathioprine, cyclophosphamide, intravenous immunoglobulin, methotrexate, mitoxantrone, or mycophenolate mofetil) was not considered a switch.
  – Therapy change after a second MS event was not considered a switch for this analysis.
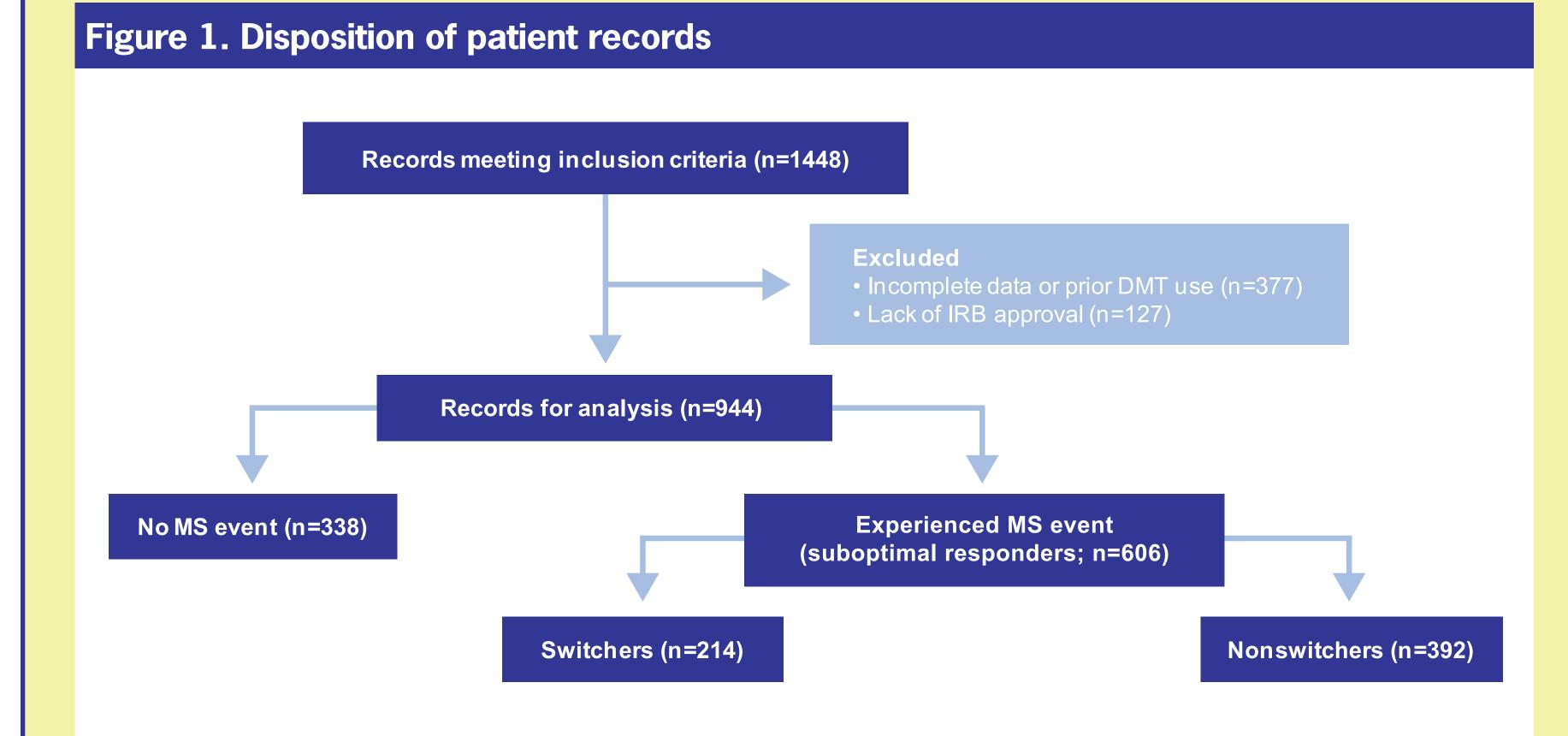► Nonswitchers were defined as those remaining on their initial DMT for ≥6 months after an MS event.

Analysis

► Predictors of DMT switching were identified using regression modeling with switching as the outcome variable and adjusted for age at the time of DMT initiation, EDSS at DMT initiation, duration from enrollment to DMT initiation, duration from DMT initiation to first MS event, and switching likelihood per MS center.

RESULTS

Patients

► Of 1448 records meeting patient selection criteria, 377 were excluded because DMT use before enrollment was unknown or chart reviews were incomplete, and 127 were excluded because of lack of institutional review board approval to extract further data from the medical charts (Figure 1).

Figure 1. Disposition of patient records

DMT=disease-modifying therapy; IRB=institutional review board; MS=multiple sclerosis.

► The mean (SD) time from the first MS event to most recent follow-up was 33.4 (27.0) months for nonswitchers and 31.8 (29.1) months for switchers (P=0.501).
► Switchers were younger at symptom onset, diagnosis, and treatment initiation than nonswitchers (Table 1).

Table 1. Demographic and clinical characteristics for DMT suboptimal responders

Characteristic*	All suboptimal responders (N=606)	Nonswitchers (n=392)	Switchers (n=214)	P
Women, %	77.4	76.5	79.0	0.492
Age at symptom onset, y	32.64 (8.9)	33.3 (8.8)	31.4 (9.1)	0.012
Age at DMT initiation, y	40.9 (9.2)	42.1 (9.3)	38.7 (8.8)	<0.001
Enrollment to DMT initiation, y	0.7 (1.3)	0.9 (1.5)	0.4 (0.9)	<0.001
DMT initiation to switch, y	—	—	3.4 (2.7)	
EDSS at DMT initiation	2.3 (1.6)	2.3 (1.6)	2.4 (1.6)	0.598

DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale.
*Values are mean (SD) unless otherwise noted.

► MRI worsening alone and EDSS worsening alone were more frequent in switchers than in nonswitchers, whereas combinations of MS events (1 relapse plus EDSS worsening; 1 relapse plus MRI worsening; or 1 relapse plus MRI and EDSS worsening; events could be concomitant) were more common in nonswitchers (Table 2).
  – Combinations of MS events that included ≥2 relapses were more frequent in switchers.

Table 2. MS events in patients with a suboptimal response to DMT

MS Event, %	All suboptimal responders (N=606)	Nonswitchers (n=392)	Switchers (n=214)
EDSS worsening alone	25.2	21.4	32.2
Relapse alone	21.5	23.2	18.2
MRI worsening alone	16.2	7.7	31.8
Relapse and EDSS worsening	15.8	22.2	4.2
Relapse, EDSS worsening, and MRI worsening	8.7	12.5	1.9
Relapse and MRI worsening	6.3	7.9	3.3
EDSS and MRI worsening	6.3	5.1	8.4

DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; MRI=magnetic resonance imaging; MS=multiple sclerosis.

Switch Predictors

► MRI worsening alone was the strongest predictor of switching; patients with MRI worsening alone were 6.3 times more likely to switch as patients with 1 relapse (95% CI, 3.1–12.9; Table 3).
  – Among patients with MRI worsening alone, the mean time between DMT initiation and first MS event was longer in the switch group than in nonswitchers (62.3 vs 38.5 months).
► EDSS worsening alone or EDSS plus MRI worsening nearly tripled the odds of switching compared with 1 relapse.
► Patients with ≥2 relapses as a first event following DMT initiation were 2.8 times more likely to switch compared with a single relapse.
► Patients were less likely to switch therapy if they experienced combinations of 1 relapse plus EDSS worsening and 1 relapse plus EDSS worsening plus MRI worsening vs 1 relapse alone.
  – Patients with the combination of 1 relapse and EDSS worsening had a longer mean time from DMT initiation to first MS event in the nonswitch group vs the switch group (26.5 vs 18.5 months).
  – Combinations of ≥2 relapses plus EDSS worsening and/or MRI worsening did not predict switch behavior, but the sample size was small.

Table 3. Predictors of DMT switching

Event or characteristic	Odds Ratio* (95% CI)	P
1 relapse (reference)	N/A	
≥2 relapses	2.8 (1.1–7.3)	0.040
EDSS worsening alone	2.2 (1.2–4.1)	0.009
MRI worsening alone	6.3 (3.1–12.9)	0.000
Combination of EDSS and MRI worsening	2.5 (1.1–5.9)	0.031
Combination of 1 relapse plus EDSS and/or MRI worsening	0.25 (0.12–0.52)	0.000
Combination of ≥2 relapses plus EDSS and/or MRI worsening	0.62 (0.24–1.6)	0.338
Time from EDSS worsening to DMT initiation	1.1 (0.96–1.3)	0.060
Time from DMT initiation to first MS event	1.0 (0.99–1.1)	0.120
Less likely to be in the switch group†	0.5 (0.31–0.73)	0.001
Time from enrollment to DMT initiation‡	0.62 (0.50–0.77)	0.000
Age at DMT initiation§	0.46 (0.30–0.71)	0.000

DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; MRI=magnetic resonance imaging; MS=multiple sclerosis.
*Logistic regression adjusted for age and EDSS at DMT initiation, duration from enrollment to DMT initiation, duration from DMT initiation to first MS event, and physician center.
† Switching likelihood per MS center (dichotomous variable; more or less likely).
‡As time gets longer, patients are less likely to switch.
§As patients get older, they are less likely to switch.

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