Assessing the Impact of Fingolimod Adherence on Relapse and Costs Using Marginal Structural Models

Le H. Hua[1], Roshani Shah[2], Gina Mavrikis Cox[2], Tim Bancroft[3], Rachel Halpern[3], Miriam G. Cisternas[3]

[1]Cleveland Clinic, Las Vegas, NV, USA; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [3]Optum, Eden Prairie, MN 55344

Background

- Disease modifying therapies (DMTs) are associated with improved long-term outcomes for RRMS patients;[1] however, within 1 to 5 years of initiation, 25% to 40% of patients discontinue DMT.[2]
- Published real-world studies demonstrate lower risk of relapses, reduced MS-related utilization, and lower MS-related costs for DMT-adherent patients compared with non-adherent patients.[2,3,4]
  - These studies may be subject to potential simultaneity bias because adherence to DMTs and the outcomes of interest are measured and analyzed over the same time period.
- Marginal structural models (MSM) mitigate simultaneity bias by measuring the impact of adherence on outcomes in subsequent periods.[5]

Objective

- The study objective was to explore the relationship between fingolimod adherence and clinical and economic outcomes among adult DMT-naïve patients who initiated treatment with fingolimod using MSM.

Methods

Study Design

- This retrospective observational study included claims for commercial and Medicare Advantage with Part D (MAPD) enrollees initiating fingolimod between 1 January 2012 and 10 May 2018. The date of the first fingolimod prescription fill was the index date.
- The 6-month pre-index period, ending the day before the index date, was used to assess demographic and clinical characteristics.
- The 18-month post-index period started on the index date.
  - The first 6 months (initiation period) were used to assess MS symptoms and adherence, allowing for time necessary for fingolimod to reach full clinical effect.[6]
  - Months 7 – 18 (post-initiation period) were used to measure adherence and outcomes.

Sample Selection

- Included patients were ≥18 years old during the index year with continuous enrollment with medical and pharmacy benefits for at least 6 months (180 days) pre-index and at least 18 months (540 days) post-index.
- Patients were required to have ≥1 medical claim with an MS diagnosis code (ICD-9-CM 340.xx or ICD-10-CM G35.xxx) in any position during pre- or post-index periods and ≥1 claim with a National Drug Code (NDC) for fingolimod after the index date (i.e., 1 – 539 days post-index).
- Patients with fingolimod NDCs on medical claims during the post-index period were excluded, as were patients with ≥1 pre-index pharmacy or medical claim for any other MS DMTs available during the study period (alemtuzumab, daclizumab, dimethyl fumarate, glatiramer acetate, IFNβ-1a, IFNβ-1b, natalizumab, ocrelizumab, peginterferon beta-1a, and teriflunomide).

Study Measures

Study measures are summarized in Table 1.

Table 1. Key Study Variables

Type	Measure	Time Period		
		Pre-Index /Index Date	Initiation (Q1/Q2)	Post-Initiation (Q3 - Q6)
Patient characteristics	**Age***	X		
	Health insurance type (MAPD vs. Commercial)*	X		
	Gender*	X		
	Comorbid conditions* (top 20 Clinical Classification Software condition categories)[7]	X		
	Medications to treat MS-related symptoms*† (anxiety, bladder dysfunction, bowel dysfunction, depression, fatigue, gait, pain, sexual dysfunction, and spasticity)	X	X	X
Adherence	**Adherence*†:** proportion of days covered (PDC) ≥0.80. PDC represents the proportion of days during the time period that the patient possessed fingolimod.		X	X
Outcomes	**MS relapse** was adapted from a validated algorithm.[8,9] *†	X	X	X
	MS-related healthcare resource utilization (HRU): inpatient† and emergency department (ED) † admissions, measured from medical claims with MS diagnosis code in any position		X	X
	All-cause healthcare costs in 2019 $US[10] comprised patient- and plan-paid costs, categorized as medical, pharmacy, and total (medical + pharmacy) costs. Total costs were measured including and excluding costs of fingolimod.		X	X

*Time-invariant covariate incorporated in MSM weights
†Time-dependent covariate incorporated in MSM weights

Methods (continued)

Statistical Analysis

- Pre-index, initiation, and post-initiation variables were analyzed descriptively across the 6 periods: pre-index, initiation, and each quarter of the 12-month post-initiation period. Q3=months 7-9, Q4=months 10-12, Q5=months 13-15, and Q6=16-18 months.
- MSM was used to estimate the effect of fingolimod adherence on: any relapse, occurrence and number of MS-related ED visits, occurrence of any MS-related inpatient admission, and all-cause costs during the 12-month post-initiation period. These models adjusted for time-dependent confounders by applying the weights incorporating variables listed in Table 1.
- Post-initiation relapse, MS-related ED visit, and inpatient admission logistic model results are presented as odds ratios (ORs). MS-related ED visit negative binomial regression result is presented as a rate ratio (RRs). All-cause medical and total cost regression results are presented as cost ratios (CRs).

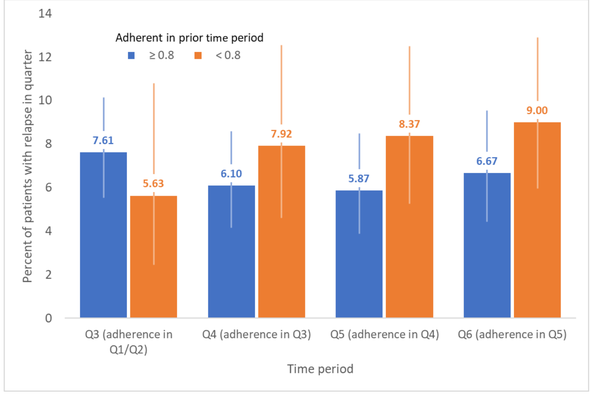
Results

From 5,413 patients identified with pharmacy claims for fingolimod during the identification period, 694 patients met the all selection criteria.

Descriptive Analysis

- Pre-index characteristics
  - The mean (SD) age of the study participants was 44.3 (10.9) years as of the index year; 76% were female.
  - The majority of patients (81%) were commercially insured.
  - Approximately half of patients (49%) exhibited other nervous system disorders, including sleep disorders, pain, inflammatory and toxic neuropathy, and eye disorders.
- The percent of patients who were adherent decreased steadily from 80% during the initiation period to 58% at Q5 and then essentially remained unchanged in Q6 at 59%.
- Relapse (Figure 1)
  - In Q3, 8% of initiation period adherent patients had at least 1 relapse whereas 6% of non-adherent patients had at least 1 relapse.
  - Starting in Q4, the direction of the association between proportion of patients with relapse and adherence in the prior period reversed.

Figure 1. Proportions and 95% Confidence Intervals of Patients with Relapse by Adherence in Prior Period



Abbreviations – Q=quarters

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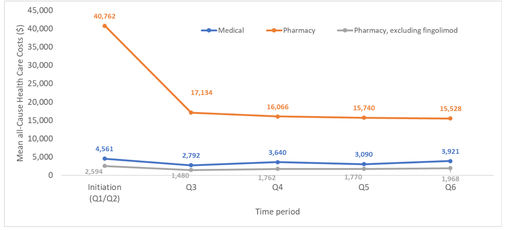
Results (continued)

Descriptive Analysis (continued)

- During the initiation period, total all-cause healthcare costs including fingolimod were $45,323; excluding costs for fingolimod, they were $7,156 (Figure 2).
- Lower values were observed for medical costs and pharmacy costs including fingolimod over the post-index quarters compared with the initiation period.

Figure 2. All-Cause Healthcare Costs over Time by Category of Spending

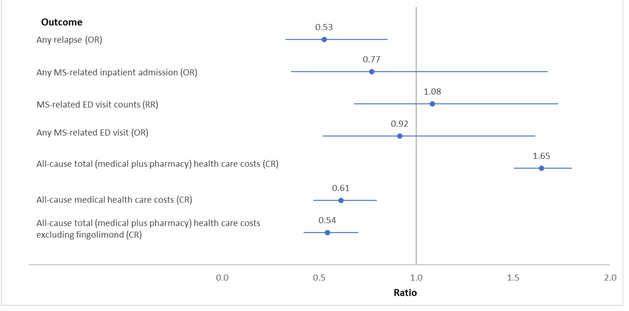


Abbreviations – Q=quarters

MSM Regression Analysis (Figure 3)

- Adherent patients had 47% lower odds of relapse than non-adherent patients (odds ratio [OR] 0.526 ; p=0.009).
- Post-initiation all-cause medical costs for patients who were adherent in the post-initiation period were 39% lower than for those who were not (cost ratio [CR] 0.612, p<0.001).
- Because the costs of fingolimod represent a large proportion of total (medical plus pharmacy) costs, total all-cause costs were higher for adherent vs. non-adherent patients (CR 1.647, <0.001).
  - When fingolimod costs were removed, adherent patients had 46% lower total costs (CR 0.543, p<0.001).

Figure 3. MSM Ratio Estimates* and 95% Confidence Intervals of Post-Initiation Adherence for All Outcomes



*Estimates for the effect of adherence on each outcome were derived from separate MSM models that adjusted for time-dependent confounders
Abbreviations. CR=cost ratio; ED=emergency department; OR=odds ratio; RR= rate ratio

Limitations

- Measures of PDC are inexact; filling a prescription does not guarantee the medication was taken as prescribed.
- MS-related symptoms could not be measured directly and were identified using claims recording prescription fills/provider administration of medications commonly used to treat symptoms.
- Race, ethnicity, socioeconomic status, and other unobserved variables may affect adherence or outcomes, but were not included in the analyses.
- Sample patients were covered by MAPD and commercial care plans; therefore findings may not apply to patients with other types of insurance coverage or uninsured patients.

Conclusions

- Adherence to fingolimod predicted lower odds of relapse and lower total all-cause costs when the cost of fingolimod was excluded.

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Disclosures

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