Association Between Adherence to Multiple Sclerosis (MS) Disease Modifying Drug (DMD) Therapy and Moderate to Severe Relapses in a Cohort of Commercial Members Followed for Three Years

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Background

- Clinical relapses in multiple sclerosis (MS) are acute, symptomatic exacerbations that can feature many different symptoms, reflecting potential involvement of different parts of the central nervous system.[1]
  - About 85% of patients with MS present with a Relapsing Remitting (RR) disease course (phenotype), lasting around two decades, in which relapses are a key feature.
  - In the subsequent Secondary Progressive (SP) phase, relapses may still occur, but the dominant feature is relentless accumulation of irreversible neurologic damage.[2,3]
- Relapses are believed to result from flair-ups of localized autoimmune processes.[4]
  - New brain and/or spinal cord lesions can be detected by Magnetic Resonance Imaging (MRI) in association with most clinical relapses.[5]
  - However, new MRI lesions appear at a rate at least 10 times higher than relapses.[6]
- Standard treatment for more serious relapses is high dose glucocorticoid therapy.
  - Typically, this is administered as intravenous methylprednisolone (IVMP) for three to five days.[7,8] Patients who don't respond to IVMP may be treated with adrenocorticotropic hormone (ACTHar® Gel). Severe relapses may result in hospitalization.
  - A detailed analysis of the components of claims cost, in 2002 dollars, for management of acute relapses found a per relapse average cost of: $12,870 for "high-intensity management," defined as hospitalization and resulting subsequent care; $1,847 for "moderate-intensity management," defined as outpatient treatment that included IVMP; and $243 for "low-intensity management," defined as physician office visits and symptom-related medications.[9]
- In clinical trials of disease modifying drugs (DMDs) for RRMS, primary outcomes have been measures of clinical relapses such as the annualized relapse rate (ARR).[10] New MRI lesions have been a secondary outcome.
- More than a dozen different DMDs have been approved by the Food and Drug Administration (FDA) for RRMS based on evidence that they reduce the rate of relapses and new lesions.
- Poor adherence to, or discontinuation of, DMD therapy may reduce its clinical benefit.
  - Administrative claims data provide a means of assessing real-world DMD adherence.
  - There are no diagnosis codes that identify relapses. However, studies have applied algorithms to administrative claims that use MS hospitalizations or outpatient treatment with IVMP as evidence of relapse.[11,12]

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Objective

- To determine:
  1) DMD member adherence;
  2) MS moderate to severe relapse; and
  3) association between relapse and DMD adherence measured through the proportion of days covered (PDC).

Methods

- From a monthly average of 15 million commercially insured members, we identified all members who were continuously eligible from October 2013 through September 2017 (four years) and younger than 65 years as of September 30, 2017, with two or more inpatient or three or more outpatient medical claims with an MS diagnosis code and who had a pharmacy (Rx) or medical claim for an FDA-approved MS DMD between October 2013 and September 2014 (year 0).
- MS DMD PDC over October 2014 to September 2017 (years 1 to 3) was determined from claim dates and days supply on Rx or assumed for medical drug claims based on manufacturer's dosing recommendations. The cohort was stratified into DMD adherent (PDC 80% or higher) and not adherent (PDC less than 80%), switching DMD was allowed.
- Claims evidence of a relapse was defined as any of three types of claims:
  - Outpatient medical claims with the Healthcare Common Procedure Coding System (HCPCS) code for IVMP;
  - Pharmacy or medical claims for ACTH; or
  - Inpatient medical claims with a diagnosis-related group (DRG) code for MS;
  - Individual "events" were identified as one of these claims with no claim meeting criteria for a relapse in the 30 preceding days.
- Quantification of relapses and relative risk of relapse:
  - The incidence of relapse from any of the three types of claims are described as the number of distinct patients meeting criteria. Annualized relapse rate (ARR) was also determined by dividing the total number of relapse events divided by the number of MS patients in the group and the number of years of observation (three).
  - The relative risk of relapse for the DMD adherent versus not adherent groups (abstract 2) was determined using an odds-ratio for any relapse with 95% confidence limits reported.[13]
- Expense is the sum of insurer and member payments ("allowed amount") without adjustment for rebates or coupons.

Results

- There were 4,813 MS members with a DMD claim between October 2013 and September 2014 (year 0). We excluded 60 of these members from analysis because they also had claims for rituximab during the subsequent three-year follow-up interval (years 1 to 3) and we wanted to study the association of relapses with adherence to FDA-approved DMDs without interference from the effects of off-label treatment of MS using rituximab. This left a final sample of 4,753 MS members with a history of a DMD.
  - In the three-year follow-up period, 2,859 (60.2%) were adherent (DMD PDC 80% or higher) and 1,894 (39.8%) were not adherent to FDA-approved DMD therapy.
  - The adherence measure was for "any DMD" with switching allowed. Over the three-year adherence assessment period, the mean number of different DMDs used was 1.39 for the adherent and 1.48 for the not adherent groups.
  - The mean age of the adherent group was 50.5 years and 75.1% were female. The mean age of the not adherent group was 48.7 years and 77.2% were female.
- **Table 1** shows the number of distinct MS members with any of the three categories of claims defined as markers of a moderate to severe relapse: IVMP, ACTH or hospitalization billed with an MS DRG.
  - 520 of the 2,859 (18.2%) adherent members compared with 471 of the 1,894 (24.9%) not adherent had one or more relapses over three years. The odds ratio was significant at 0.672 (95% confidence interval 0.584 to 0.774). This means that adherent members had about a third lower risk of having at least one relapse over three years.
  - The observed risk reduction of 6.7% for any moderate to severe relapse in three years (24.9% minus 18.2%) results in a calculated number needed to treat (NNT) of 15 members. If the observed association is causal, this finding implies that, on average, achieving adherence to DMD therapy for 15 not adherent MS members for three years might prevent one member from having a moderate to severe relapse.
- The summed expense for IVMP, ACTH and MS inpatient stays for the 991 members shown in **Table 1** was $8,786,612, a mean cost of $8,866 per patient with any relapse in three years. The cost of DMD therapy for 15 patients would be $3,075,000 to cover 80% of days over three years (at $234/covered day, the observed cost in a companion study[13]) or $205,000 per patient for three years.
- **Table 2** and **Figures 1a** and **1b** stratify percentage of patients with a moderate to severe relapse in three years and the ARR by age groups.
  - The finding that relapse rates decrease with age in both adherent and non-adherent groups is consistent with a study of MS natural history that found relapse rate decreases both with time since diagnosis and with patient age.[14]
  - The observed ARRs of 0.123 for MS members DMD adherent versus 0.183 for those not adherent are lower than those that have been reported from most clinical trials. In a review of 55 trials, median ARR was 0.6.[15]
    - The clinical trials have more accurate and complete identification of relapse events, including milder events managed in the physician office setting, which would not result in the sorts of claims we used to identify relapses.
    - A second difference is that clinical trials have typically included patients who are younger and likely more recently diagnosed. The mean age in those 55 trials was 35 years while the mean age in this study was 49 years.
  - The observed ARRs in our study are also lower than those reported in two published studies that used administrative claims to identify MS relapses.[14,15] These studies included mild relapses identified using pharmacy claims for glucocorticoids, but do not describe their methods sufficiently to replicate nor do they report what fraction of relapses were mild.

Table 1. Multiple Sclerosis (MS) Members with Claims Evidence of a Relapse During Three Years of Follow-up, Stratified by Adherence to Disease Modifying Drug (DMD) Therapy

	During three-year follow-up, October 2014 to September 2017			
MS relapse event category	Adherent to DMD† N = 2,859	Non-adherent to DMD† N = 1,894	Odds ratio (95% confidence interval)	P-value
Members with an outpatient IVMP claim	463 (16.2%)	426 (22.5%)	0.666 (0.575 to 0.771)	<.0001
Members with an ACTH claim	32 (1.1%)	19 (1.0%)	1.116 (0.631 to 1.974)	0.8231
Members with an MS inpatient stay	85 (3.0%)	106 (5.6%)	0.517 (0.386 to 0.692)	<.0001
Total members with a moderate to severe relapse event*	520 (18.2%)	471 (24.9%)	0.672 (0.584 to 0.774)	<.0001

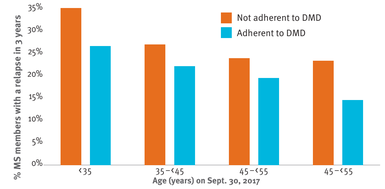
IVMP = intravenous methylprednisolone; ACTH = adrenocorticotropic hormone (ACTHar®); MS inpatient stay = hospital inpatient claim with diagnosis-related group (DRG) code for MS
*During 3 years follow-up, members with a moderate to severe relapse = number of unique MS members with an IVMP, ACTH or MS inpatient claim.
†Adherent was defined as proportion of days covered (PDC) +/− 80%, by any DMD with switching allowed, during three years of follow-up (years 1 to 3), all members were continuously enrolled and had a DMD claim the prior year (year 0).

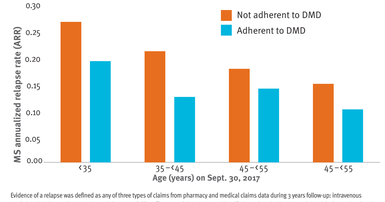
Table 2. Multiple Sclerosis (MS) Members with any Moderate to Severe Relapse and Annualized Relapse Rate by Disease Modifying Drug (DMD) Adherence and Member Age

	During three-year follow-up, October 2014 to September 2017							
	MS members		MS members with any relapse		Number of relapses		Annualized relapse rate (ARR)	
Age (years)	Not adherent to DMD	Adherent to DMD	Not adherent to DMD (%)	Adherent to DMD (%)	Not adherent to DMD	Adherent to DMD	Not adherent to DMD	Adherent to DMD
<35	166	146	57 (34.3%)	38 (26.0%)	131	83	0.263	0.189
35–<45	476	603	125 (26.3%)	130 (21.6%)	297	221	0.208	0.122
45–<55	686	1,092	160 (23.3%)	207 (19.0%)	361	451	0.175	0.138
55–<65	566	1,018	129 (22.8%)	145 (14.2%)	250	304	0.147	0.099
Total	**1,894**	**2,859**	**471 (24.9%)**	**520 (18.2%)**	**1,039**	**1,059**	**0.183**	**0.123**

Adherent = >= 80% of days covered by any DMD during three-year follow-up period; Age = age as of Sept. 30, 2017;
Annualized relapse rate = number of relapses divided by number of members in cohort times three years
Note: Some MS members had more than one moderate to severe relapse.

Figure 1a and 1b. Percentage of Multiple Sclerosis (MS) Members with any Moderate to Severe Relapse and the Annualized Relapse Rate by DMD Adherence and Member Age





Evidence of a relapse was defined as any of three types of claims from pharmacy and medical claims data during 3 years follow-up: intravenous methylprednisolone; adrenocorticotropic hormone (ACTHar®); or an MS inpatient stay identified as a hospital inpatient claim with diagnosis-related group (DRG) code for MS.
Adherent was defined as proportion of days covered (PDC) +/− 80%, by any DMD with switching allowed, during three years of follow-up (years 1 to 3), all members were continuously enrolled and had a DMD claim the prior year (year 0).

Conclusions

- Six of 10 MS commercially insured members with a DMD claim in the first year of the study remained adherent to DMD therapy over three years follow-up.
  - Three years of DMD adherence was associated with a statistically significant seven percentage point lower incidence of members with claims indicating a moderate to severe clinical relapse.
  - If the observed association is causal, this finding implies that, on average, improving adherence to DMD therapy for 15 not adherent MS members for three years would be expected to prevent one member from having a moderate to severe relapse.
  - A DMD cost of $3 million to obtain adherence in 15 members would be expected to save $9,000 in direct medical costs from avoidance of moderate to severe relapses for one MS patient. An investment of $333 to save $1 in direct medical costs.
  - DMDs also reduce the rate of occurrence of mild relapses and new MRI lesions that are not associated with clinical relapses, and may delay progression of MS. Therefore, full accounting of the direct and indirect cost savings from DMD therapy likely exceeds the direct cost savings estimated in this study.
- The value of treating more MS members with DMDs or improving adherence needs to be assessed from a societal perspective and with a time horizon of many years. Multiple studies attempting to assess the total value of DMD therapy have concluded that use of MS DMDs greatly exceeds conventional thresholds for cost-effectiveness without large reductions in the prices of these drugs.[16,17]

Limitations

- This study uses only information from administrative claims to determine which members have MS and deduces clinical relapses from procedure codes, since there are no diagnosis codes for acute exacerbations of MS. We could not identify milder relapses that were managed in outpatient settings with therapies other than IVMP or ACTH.
- Adherence is assessed using claims data and may inaccurately identify a member as adherent or non-adherent. In addition, the adherence cut point of 80% or greater proportion of days covered is an arbitrary adherence determinate.
- Costs attributed to relapses were limited to direct, claim line expenses. However, relapses also have significant indirect and intangible costs and an association, not well characterized, with long-term outcomes.
- These findings are limited to commercially insured members who were continuously enrolled for four years and may not be representative of the general population with MS or those taking DMDs.

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