Poster P489

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Real-world Change in Annualized Relapse Rate Following Initiation of Ofatumumab in Patients with Multiple Sclerosis

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KEY FINDINGS & CONCLUSIONS

- In a real-world sample of patients with multiple sclerosis, annualized relapse rate in the year prior to ofatumumab initiation was five times higher than in the year following ofatumumab initiation.
- The substantial reduction in relapse rate following ofatumumab initiation was also observed in a subset of patients without prior anti-CD20 exposure.
- Results align with clinical trial evidence of ofatumumab's efficacy in reducing relapse incidence in multiple sclerosis.

INTRODUCTION

- Multiple sclerosis (MS) is a chronic, irreversible autoimmune disease of the central nervous system[1] that affects close to 1 million US adults.[2]
- Currently, no curative treatment exists for MS. However, several disease-modifying therapies (DMTs) were shown to reduce relapse rates, slow disability worsening, and disease progression.[3]
- Ofatumumab (OMB) is an FDA-approved CD20-directed monoclonal antibody that has demonstrated efficacy in reducing incidence of relapse in multiple sclerosis (MS) within clinical trials. Real-world (RW) data are needed to ascertain OMB's effectiveness in reducing relapse in a broader population of patients with MS outside of clinical trials.

OBJECTIVE

- To evaluate the change in annualized relapse rate (ARR) following initiation of OMB in a RW sample of patients with MS using U.S. administrative claims data, overall and in a sub-cohort of patients without prior exposure to anti-CD20 therapies.

METHODS

Study Design

- A retrospective pre-post cohort study was conducted using Optum® Clinformatics® Data Mart Database (Aug 2019-May 2023; ***study period***), a longitudinal database of medical and pharmacy administrative claims for patients enrolled in commercial insurance and Medicare Advantage plans in the US.
- ***Index date*** = the date of the first OMB claim, which was by design after FDA approval on 08/20/2020
- The ***OMB MS sample*** included adults (age ≥18) with:
  - ≥1 MS diagnosis;
  - ≥1 OMB claim on or after 08/20/2020 (index date);
  - Continuous enrollment in a healthcare plan from 12 months before to 12 months after index date; and
  - OMB persistence in the 12 months post-index date (i.e., no OMB gaps of >60 days or treatment switch).
- The ***anti-CD20-naïve sub-cohort*** included a subset of the OMB MS sample without a claim for another anti-CD20 within the 12 months prior to the index date.
- ARR was measured in two periods:
  - ***Pre-index period*** = fixed 12-month period prior to index date;
  - ***Post-index period*** = varying ≥12-month period from index date until end of enrollment/study period.

Measurements

- ***Relapse*** was defined using a validated claims-based algorithm[4] as an inpatient (IP) admission with primary MS diagnosis or outpatient (OP) or emergency department (ED) visit with MS diagnosis in primary or secondary position with a claim for high dose oral corticosteroids, intravenous methylprednisolone, corticotropin, or plasma exchange within 7 days. The first relapse event started at the earliest between the IP admission date for an IP-based relapse indicator, the service date of the OP claim for an OP-based relapse indicator, or the date of ED visit. Multiple qualifying relapse events within 30 days were collapsed into a single relapse episode. For example, three qualifying OP visits, each 15 days apart, would be considered as a single relapse episode.

Statistical Analysis

- ARRs and their 95% confidence intervals (CIs) were obtained from intercept-only negative binomial (NB) models. Results are presented as ARR (95% CI; N relapse episodes / N person-years).
- Incidence rate ratios (IRR) comparing ARR in the pre- and post-periods were obtained from NB models with period (post- vs. pre-index) as a predictor variable, standard errors adjusted for clustering by patient ID, and no covariate adjustment. Covariate adjustment was not applied in the analysis as patient-level confounders were controlled by the within-individual pre-post design.

RESULTS

Pre-index Patient Characteristics

- 342 patients met inclusion criteria for the OMB MS sample
- 291 patients met additional inclusion criteria for the anti-CD20 naïve sub-cohort.
- Among patients in the OMB MS sample, mean (standard deviation [SD]) age at index date was 49 years (10.9) (**Table 1**). Age at index date varied widely, ranging from 21 to 78 years. Most (75%) patients were female, 66% were White, and 33% were enrolled in a Medicare Advantage plan.
- Included patients had relatively mild MS disability, with 87% of patients having no or mild EDSS-related symptoms. However, MS disability may be underestimated in claims data (see Limitations). The most common MS-related symptoms and secondary conditions were fatigue or malaise (33%), anxiety (33%), and sensory problems (25%). The mean Deyo-Charlson Comorbidity Index (DCCI) value of 0.8 indicates a relatively low level of comorbidity burden in the sample.
- Patient characteristics were in general similar between the OMB MS sample and anti-CD20-naïve sub-cohort.

Table 1. Pre-index Patient Characteristics

	OMB MS sample N = 342	Anti-CD20-naïve sub-cohort N = 291
Age		
Mean (SD)	48.79 (10.94)	49.10 (10.93)
Median (range)	48.48 (21.37, 77.80)	48.70 (21.37, 77.80)
Female, n (%)	258 (75.44)	219 (75.26)
Payer type, n (%)		
Commercial	228 (66.67)	195 (67.01)
Medicare	114 (33.33)	96 (32.99)
Year of index date		
2020	18 (5.26)	17 (5.84)
2021	233 (68.13)	194 (66.67)
2022	91 (26.61)	80 (27.49)
Race, n (%)		
White	225 (65.79)	194 (66.67)
Black or African American	48 (14.04)	43 (14.78)
Hispanic	39 (11.40)	28 (9.62)
Asian	5 (1.46)	4 (1.37)
Missing	25 (7.31)	22 (7.56)
Region, n (%)		
Midwest	88 (25.73)	75 (25.77)
Northeast	36 (10.53)	32 (11.00)
South	151 (44.15)	129 (44.33)
West	67 (19.59)	55 (18.90)
DCCI, mean (SD)	0.82 (1.33)	0.83 (1.37)
PDG index, mean (SD)	0.99 (1.10)	0.96 (1.09)
Top 5 MS-related symptoms and secondary conditions, n (%)		
Fatigue or malaise	114 (33.33)	100 (34.36)
Anxiety	112 (32.75)	90 (30.93)
Sensory problems	84 (24.56)	75 (25.77)
Eye symptoms	66 (19.30)	58 (19.93)
Urinary tract infection	51 (14.91)	40 (13.75)
MS disability[1], n (%)		
No EDSS-related symptoms	290 (84.80)	247 (84.88)
Mild	7 (2.05)	7 (2.41)
Moderate	12 (3.51)	10 (3.44)
Severe	33 (9.65)	27 (9.28)
Prior DMT, n (%)	228 (66.67)	177 (60.82)
Low/moderate efficacy therapy	154 (45.03)	150 (51.55)
High efficacy therapy	79 (23.10)	28 (9.62)

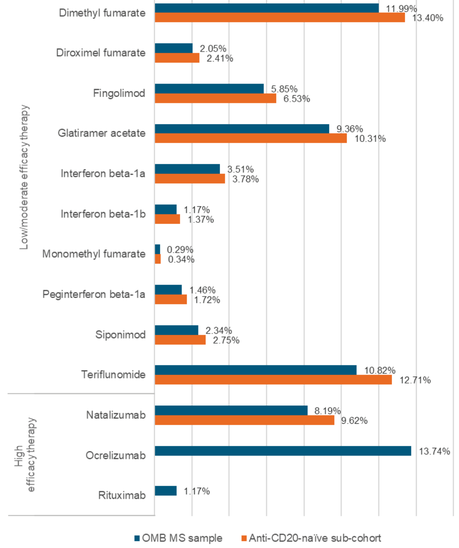
Abbreviations: DCCI: Deyo-Charlson Comorbidity Index; DMT: disease modifying therapy; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; OMB: ofatumumab; PDG: Psychiatric Diagnosis Group; SD: standard deviation.

Notes:
[1] MS disability is based on observance of EDSS-related symptoms and durable medical equipment use observed in claims data weighted by severity score. Using a published algorithm[5], disability levels and definitions are as follows: Severe = Defined as having ≥1 EDSS-related symptom with severity score = 3 in any functional system; Moderate: Defined as having ≥1 EDSS-related symptom with severity score = 2 in any functional system or having ≥2 functional systems with severity score = 1; Mild: Defined as having only one EDSS-related symptom with severity score = 1 or having no EDSS-related symptoms observed during the measurement period.

MS Treatment History

- Two thirds (67%) of patients in the overall OMB MS sample received another DMT in the pre-index period; 45% and 23% of included patients received low- and high-efficacy DMTs, respectively (**Table 1**).
- In the overall OMB MS sample, the most common DMT in the pre-index period was ocrelizumab (14%), followed by dimethyl fumarate (12%), and teriflunomide (11%) (**Figure 1**).
- In the anti-CD20-naïve sub-cohort, a higher proportion (39% vs. 33%) of patients were untreated in pre-index period (**Table 1**). The most common DMTs received were dimethyl fumarate (13%), followed by teriflunomide (13%), and glatiramer acetate (10%) (**Figure 1**).

Figure 1. Summary of DMTs in the Pre-index Period



Abbreviations: DMT: disease modifying therapy; MS: multiple sclerosis; OMB: ofatumumab.

Key Outcomes

Relapse in pre- and post-index periods

- In the overall OMB MS sample, ARR in the pre-index period was 0.43 (0.36, 0.52; 147 / 342) compared to 0.09 (0.07, 0.13; 51 / 563) in the post-index period (**Table 2**). This equated to a statistically significant 79% reduction in ARR following OMB initiation (IRR: 0.21; 95% CI: 0.16, 0.29; p<0.001) (**Figure 2**). Mean (SD) follow-up in the post-index period was 1.65 (0.43) years.
- In the anti-CD20-naïve sub-cohort, ARR in the pre-index period was 0.29 (0.23, 0.37; 85 / 291) compared to 0.08 (0.06, 0.12; 39 / 477) in the post-index period (**Table 2**). This equated to a statistically significant 72% reduction in ARR following OMB initiation (IRR: 0.28; 95% CI: 0.19, 0.42; p<0.001) (**Figure 2**).
- The lower pre-index ARR in the anti-CD20-naïve sub-cohort (0.292 vs. 0.430) suggests that prior exposure to high efficacy therapies might be an indicator of more severe or advanced disease.
- The significant reduction in ARR following OMB initiation was robust to varying the claims-based definition of relapse. For example, using an alternative claims-based algorithm[6] where IV methylprednisolone occurring within ±5 days of an ocrelizumab infusion (for which IV corticosteroids are indicated as premedication) is excluded from the definition of relapse. Similarly, the significant reduction in ARR following OMB initiation remained when using a 3- instead of 12-month persistent OMB requirement in the post-index period.

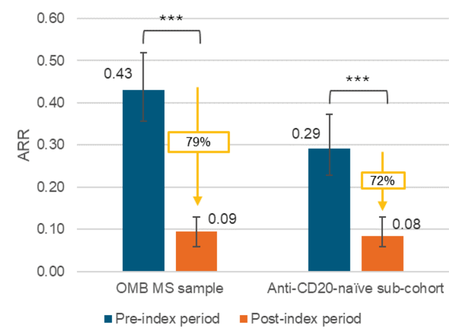
Table 2. Relapse in the Pre- and Post-index Periods[1]

	OMB MS sample N = 342			Anti-CD20-naïve sub-cohort N = 291		
	Pre-index period	Post-index period[2]	P-value[3]	Pre-index period	Post-index period[2]	P-value[3]
N relapse episodes	147	51	--	85	39	--
N person-years	342	563	--	291	477	--
ARR (95% CI)	0.430 (0.356, 0.519)	0.094 (0.068, 0.129)	< 0.001	0.292 (0.229, 0.372)	0.084 (0.059, 0.120)	< 0.001
IRR (95% CI)[3]	0.214 (0.156, 0.294)		< 0.001	0.284 (0.194, 0.416)		< 0.001

Abbreviations: ARR: annualized relapse rate; CI: confidence interval; ED: emergency department; IP: inpatient; IRR: incidence rate ratio; IV: intravenous; MS: multiple sclerosis; OMB: ofatumumab; OP: outpatient.

Notes:
[1] Per a validated claims-based algorithm[4], relapse was defined as either of the following: (1) an IP visit with an MS diagnosis (ICD-9: 335; ICD-10: G35.xx) in the primary position; (2) an OP or ED visit with an MS diagnosis in the primary or secondary position along with a claim for a high dose oral corticosteroid (≥500 mg/day), IV methylprednisolone, corticotropin, or plasma exchange within 7 days of the OP or ED visit. The first relapse event starts at the earliest between the IP admission date, the service date of the OP claim, or the date of ED visit. All qualifying IP or OP/ED visits that occurred during a single 30-day period were considered as one relapse episode. For multiple qualifying IP and OP/ED visits, provided that each successive visit occurred within 30 days of the previous visit, events were amalgamated into one relapse episode.
[2] Per eligibility criteria, all patients will have at least 12 months of continuous follow-up after index date where they are persistent on OMB. Patients are followed until the end of follow-up or end of study period, whichever comes sooner (i.e., patients can contribute more than 1 year of person-time and relapses occurring after 12 months are included).
[3] Wilcoxon signed rank test (paired) is used to compare ARR between the pre- to post-index periods. Negative binomial regression is used to estimate unadjusted rate ratios; this is done by stacking the pre- and post-index periods and including an indicator for period as a covariate in the model. Statistical significance and 95% CIs are based on standard errors clustered around the patient ID to account for the longitudinal nature of the data. Statistical adjustment on time-invariant factors is not performed as patients will serve as their own controls.

Figure 2. Summary of Relapse in Pre- and Post-index Periods



Abbreviations: ARR: annualized relapse rate; DMT: disease modifying therapy; MS: multiple sclerosis; OMB: ofatumumab.

Notes:
*** p < 0.001

Limitations

- Analyses using claims data are dependent on the accuracy and specificity of entered diagnostic codes.
- Related to the above point, the MS disability score (**Table 1**) includes chronic conditions, which may be sporadically or inconsistently recorded in administrative claims data. The score also includes long-term DME (e.g., wheelchairs, walkers), which are typically only recorded at the time of initial claim. As such, the degree of MS disability prior to OMB initiation in the sample may be underestimated. The lack of notable difference in MS disability score between the OMB MS sample and anti-CD20-naïve sub-cohort, despite more frequent pre-index relapses in the former group (**Table 2**), may indicate a higher MS severity among patients with prior anti-CD20 exposure that is not captured in the data.
- This study uses a pre/post design that adjusts for time-invariant factors but not for time-variant factors like disease progression, which may confound results.
- The requirement of 12 months of persistent OMB use during the post-index period may introduce selection bias by removing patients who were intolerant or non-responsive to OMB. Results remained consistent in a sensitivity analysis requiring only 3 months of persistent OMB use, suggesting any bias may be minimal.
- Estimates in the pre-index period (i.e., pre-index ARR) will capture the loss or lack of effectiveness associated with the pre-index treatment that may have motivated the switch to OMB. In other words, poor or sub-optimal pre-index endpoints may be inherent to the study design.
- Data are primarily from employer-sponsored plans and therefore underrepresent patients over age 65, potentially limiting generalizability of findings.
- OMB received approval in August 2020, resulting in a relatively limited amount of real-world data available with adequate follow-up time.

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Disclosures

RT and RK are employees of STATLOG Inc., which has received funding from Novartis Pharmaceuticals Corporation. MT, QS, BB, and AG are employees of Novartis Pharmaceuticals Corporation.

References

1. Martin R, et al. (2016). Eur J Immunol, 46(9): 2078-2090. **2.** Wallin MT, et al. (2019). Neurology, 92(10): e1029-e1040. Erratum in: Neurology. 2019;93(15):688. PMCID: PMC6442006. **3.** Finkelsztejn A. (2014). Perspect Medicin Chem, 6: 65-72. PMCID: PMC4197902. **4.** Ollendorf DA, et al. (2002). J Manag Care Pharm, 8(6): 469-476. **5.** Berkovich R, et al. (2021). J Med Econ, 24(1): 46-53. **6.** Hersh CM, et al. (2022). Presented at: 38th Congress of the ECTRIMS; Amsterdam, The Netherlands.