Real-World Clinical and Economic Outcomes Among Persons With Multiple Sclerosis Initiating First- Versus Second- or Late-Line Treatment With Ocrelizumab

SUPPLEMENTARY MATERIAL

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Matching 1L and 2L+ OCR Cohorts

As described in the Methods section of the manuscript, persons with multiple sclerosis (pwMS) who initiated ocrelizumab (OCR) were categorized into either the first-line (1L) or second- or later-line (2L+) OCR cohorts based on when they initiated OCR after the first observed multiple sclerosis (MS) diagnosis code. All pwMS in the 1L and 2L+ OCR cohorts were matched 1:1 based on the length of the continuous enrollment period after the initiation of the first-line disease-modifying therapy (DMT; index date 1). This matching was used to ensure that the 2 cohorts had the same amount of follow-up time to observe outcomes of interest after index date 1. The steps used to match pwMS in the 1L OCR and 2L+ OCR cohorts are provided below.

1. Identify the full length of the continuous enrollment period from index date 1 until the end of eligibility for each person with MS. The length of this period is referred to as the "total continuous enrollment period".
2. One person with MS in the 2L+ OCR cohort is selected. The date of initiation of OCR for that person with MS in the 2L+ OCR cohort is identified (index date 2), and the length of the period between index date 1 and index date 2 is identified. This period is referred to as "follow-up period 1".
3. All pwMS in the 1L OCR cohort are selected, and their total continuous enrollment period is compared with the total continuous enrollment period for the 1 selected person with MS in the 2L+ OCR cohort.
4. Only pwMS in the 1L OCR cohort with a total continuous enrollment period at least as long as the length of follow-up period 1 for that one selected person with MS in the 2L+ OCR cohort are retained as potential matches for the one person with MS in the 2L+ OCR cohort.
5. Among all retained pwMS in the 1L OCR cohort with a long enough total continuous period, 1 is randomly selected as the match for that 1 person with MS in the 2L+ OCR cohort.
6. The process described above is completed until there are no more remaining pwMS in the 1L or 2L+ OCR cohorts who can be matched.

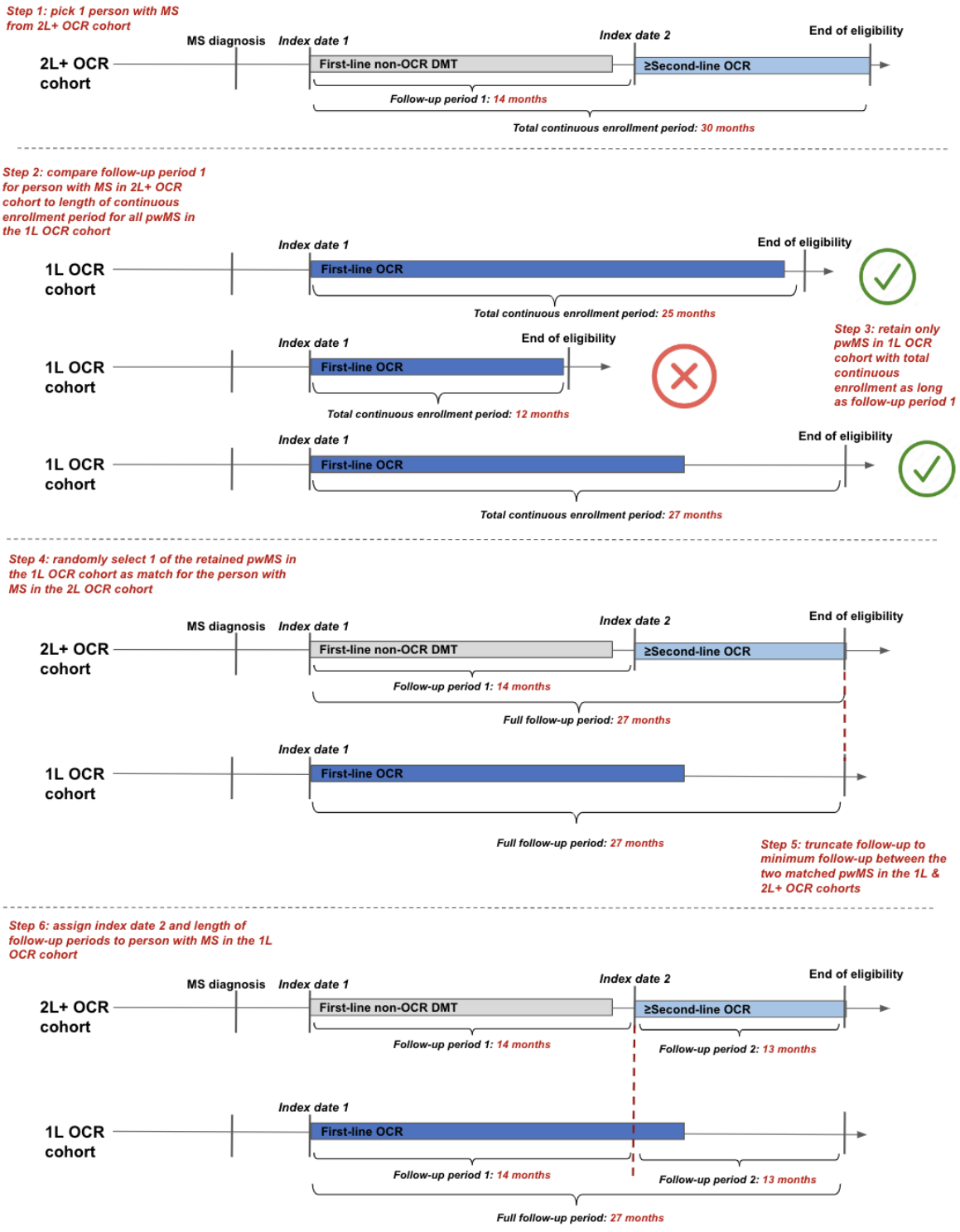
7. Among all matched pairs, the end of eligibility is truncated to the minimum of the end of eligibility within each matched pair. The period from index date 1 to the truncated end of eligibility within that pair is referred to as the "full follow-up period".
8. The full follow-up period is then divided into 2 periods in order to examine outcomes before and after the initiation of OCR initiated in the second or later-line of treatment (index date 2). For the matched pwMS in the 1L OCR cohort, index date 2 is assigned based on when their matched person with MS in the 2L+ OCR cohort initiated OCR. In both the 1L and 2L+ OCR cohorts, follow-up period 1 is the period from index date 1, and follow-up period 2 is the period from index date 2 until the truncated end of eligibility (the end of the full follow-up period).

To further illustrate this process, an example of matching a person with MS in the 2L+ OCR cohort is described below and in **Figure S1**.

1. One person with MS in the 2L+ OCR cohort was randomly selected. This selected person has a total continuous enrollment period after index date 1 of 30 months. This person with MS initiated OCR a total of 14 months after their initiation of a first-line, non-OCR DMT (index date 1). Therefore, the length of follow-up period 1 for this person is 14 months.
2. The lengths of the total continuous enrollment period for all pwMS in the 1L OCR cohort are compared with the length of follow-up period 1 for the one selected person with MS from the 2L+ OCR cohort. In this example with three pwMS in the 1L OCR cohort, the lengths of the total continuous enrollment period after index date 1 are 27, 25, and 12 months.
3. Only potential 1L OCR matches with a total continuous enrollment period at least as long as the length of follow-up period 1 for the person with MS in the 2L+ OCR cohort are retained as potential matches. Since the person with MS in the 2L+ OCR cohort had a follow-up period 1 length of 14 months, only two pwMS in the 1L cohort are retained because they had total continuous enrollment periods of 27 and 25 months.

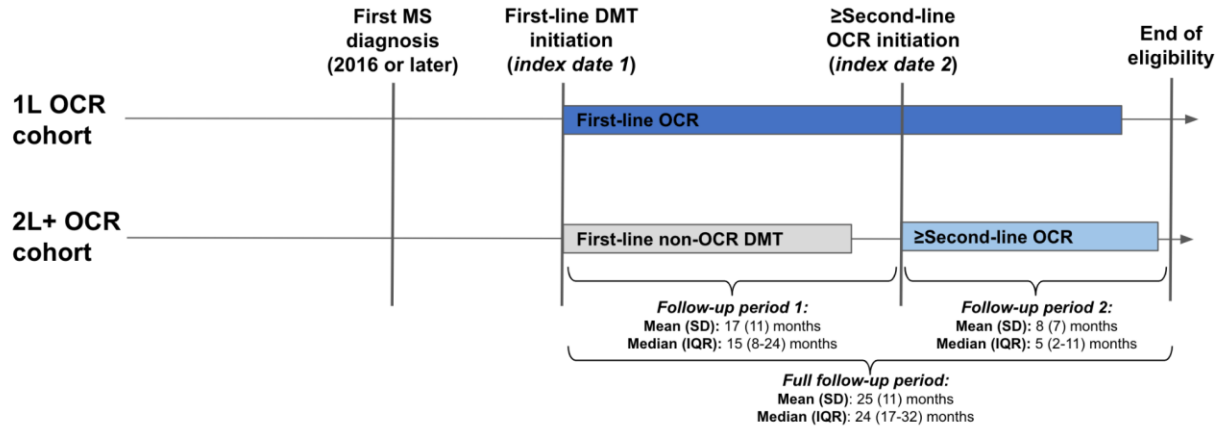
4. Among the retained pwMS in the 1L OCR cohort, 1 is randomly selected as a match for the 1 selected person with MS in the 2L+ OCR cohort. In this example, the person with MS in the 1L OCR cohort with a total continuous enrollment period of 27 months is randomly selected.
5. For the matched pair of pwMS in the 1L OCR and 2L+ OCR cohorts, the end of eligibility is truncated to the minimum for that pair. In this pair, the minimum is 27 months. Therefore, the full follow-up period for this pair is 27 months.
6. Index date 2 is then assigned to the person with MS in the 1L OCR cohort based on when the person with MS in the 2L+ OCR cohort initiated OCR. In this pair, after the assignment of index date 2, the pwMS in the 1L OCR and 2L+ OCR cohorts both have a follow-up period 1 of 14 months and a follow-up period 2 of 13 months.

Figure S1: Matching pwMS in the 1L and 2L+ OCR cohorts



1L = first-line; 2L+ = second- or later-line; DMT = disease-modifying therapy; MS = multiple sclerosis; OCR = ocrelizumab; pwMS = people with MS.

Figure S2: Length of follow-up time and number of OCR infusions



1L = first-line; 2L+ = second- or later-line; DMT = disease-modifying therapy; IQR = interquartile range; MS = multiple sclerosis; OCR = ocrelizumab; SD = standard deviation.

Table S1: First-line DMTs initiated prior to OCR among pwMS in the 2L+ OCR cohort

	2L+ OCR cohort (N=347)
First-line non-OCR DMT (*efficacy*), n (%)	
Glatiramer acetate (*low*)	110 (32)
Dimethyl fumarate (*moderate*)	95 (27)
Natalizumab (*high*)	50 (14)
Fingolimod (*moderate*)	40 (12)
Interferon beta-1a (*low*)	20 (5.8)
Teriflunomide (*low*)	18 (5.2)
Other DMTs[a,b,c]	14 (4.0)
Efficacy of first-line non-OCR DMT, n (%)	
Low efficacy	154 (44)
Moderate efficacy	136 (39)
High efficacy	57 (16)

1L = first-line; 2L+ = second- or later-line; DMT = disease-modifying therapy; MS = multiple sclerosis; OCR = ocrelizumab; pwMS = persons with MS.

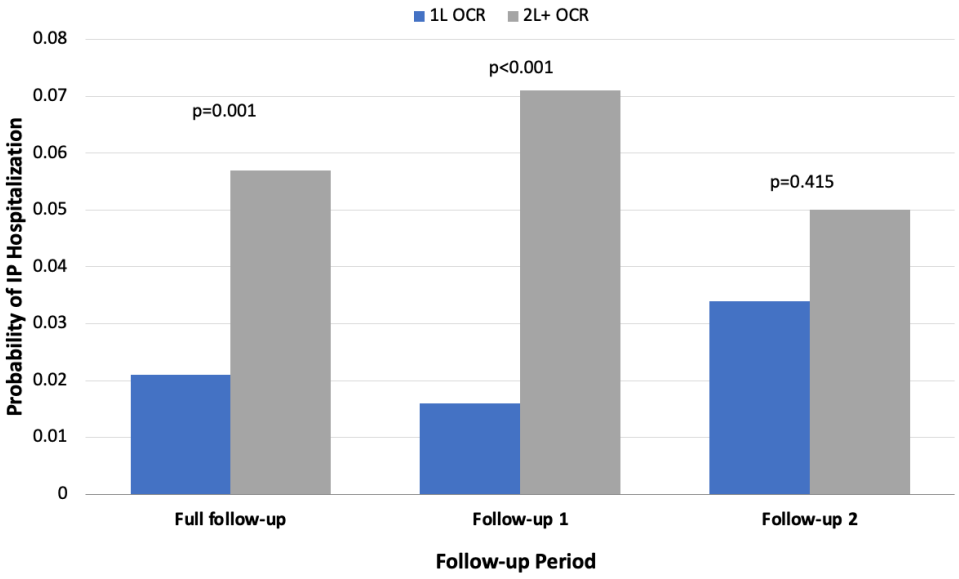
Notes:

[a] Other DMTs included rituximab (high efficacy), interferon beta-1b (low), peginterferon beta-1a (low), daclizumab (high), and siponimod (moderate). Each of these DMTs had <10 pwMS initiating that DMT as the first-line DMT after diagnosis prior to the initiation of second or later-line OCR.

[b] Rituximab is not US Food and Drug Administration–approved for the treatment of MS. However, rituximab was included in order to capture all lines of treatment and accurately classify pwMS in the 1L vs. 2L+ OCR cohorts.

[c] Daclizumab was withdrawn from the market in 2018 but was included in this study in order to capture all lines of treatment and accurately classify pwMS in the 1L vs. 2L+ OCR cohorts.

Figure S3: Probability of MS-related IP hospitalization



1L = first-line; 2L+ = second- or later-line; CI = confidence interval; DMT = disease-modifying therapy; IP = inpatient; IPT = inverse probability of treatment; MS = multiple sclerosis; OCR = ocrelizumab; pwMS = persons with MS.

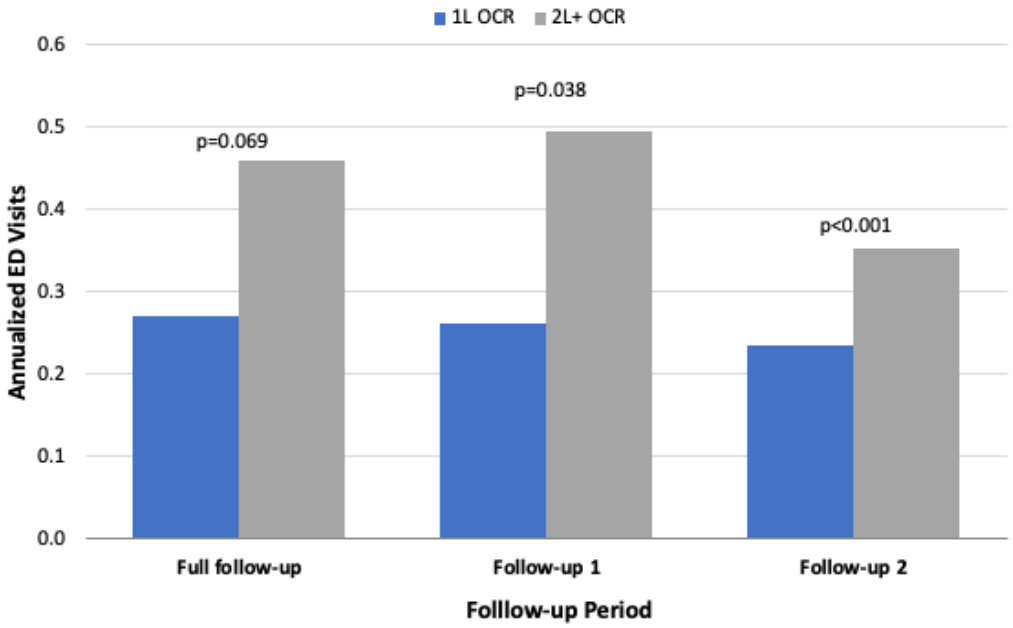
Notes:

[a] The full follow-up period includes the period from the initiation of the first-line DMT (index date 1) to the minimum of the end of continuous eligibility for each matched pair. Follow-up period 1 includes the period from index date 1 to the date of initiation of second of later-line OCR (index date 2) among pwMS in the 2L+ OCR cohort and their matched pwMS in the 1L OCR cohort. Follow-up period 2 includes the period from index date 2 to the end of the full follow-up period.

[b] MS-related IP hospitalizations included all hospitalizations with an MS diagnosis code in any position on the claim.

[c] The probability of hospitalization within 1 year was estimated in each of the follow-up periods using an IPT-weighted logistic regression with follow-up time included as an offset variable.

Figure S4: Annualized MS-related, non-DMT ED visits



1L = first-line; 2L+ = second- or later-line; CI = confidence interval; DMT = disease-modifying therapy; ED = emergency department; HCRU = healthcare resource use; IPT = inverse probability of treatment; MS = multiple sclerosis; OCR = ocrelizumab; pwMS = persons with MS.

Notes:

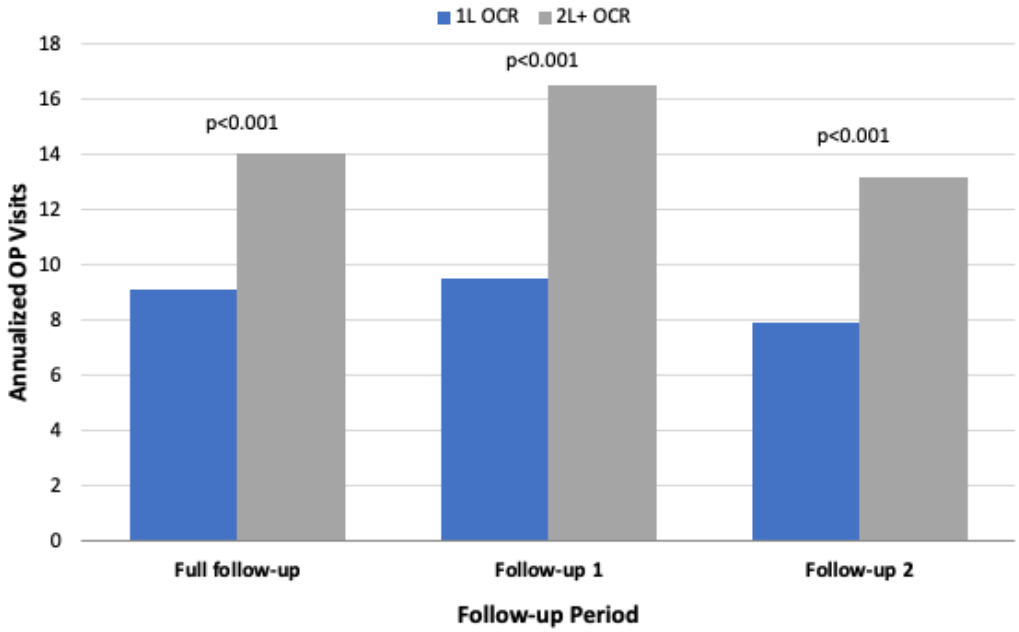
[a] The full follow-up period includes the period from the initiation of the first-line DMT (index date 1) to the minimum of the end of continuous eligibility for each matched pair. Follow-up period 1 includes the period from index date 1 to the date of initiation of second of later-line OCR (index date 2) among pwMS in the 2L+ OCR cohort and their matched pwMS in the 1L OCR cohort. Follow-up period 2 includes the period from index date 2 to the end of the full follow-up period.

[b] MS-related ED visits included all non-DMT ED visits with an MS diagnosis code in any position on the claim.

[c] Annualized ED visits were summarized in each follow-up period using stabilized IPT weights.

[d] All p-values were adjusted for multiple comparisons within each type of HCRU or cost (all-cause, non-DMT and MS-related, and non-DMT) by controlling for the false discovery rate using the Benjamini and Hochberg method.

Figure S5: Annualized MS-related, non-DMT OP visits



1L = first-line; 2L+ = second- or late- line; CI = confidence interval; DMT = disease-modifying therapy; HCRU = healthcare resource use; IPT = inverse probability of treatment; MS = multiple sclerosis; OCR = ocrelizumab; OP = outpatient; pwMS = persons with MS.

Notes:

[a] The full follow-up period includes the period from the initiation of the first-line DMT (index date 1) to the minimum of the end of continuous eligibility for each matched pair. Follow-up period 1 includes the period from index date 1 to the date of initiation of second of later-line OCR (index date 2) among pwMS in the 2L+ OCR cohort and their matched pwMS in the 1L OCR cohort. Follow-up period 2 includes the period from index date 2 to the end of the full follow-up period.

[b] MS-related OP visits included all non-DMT OP visits with an MS diagnosis code in any position on the claim.

[c] Annualized OP visits were summarized in each follow-up period using stabilized IPT weights.

[d] All p-values were adjusted for multiple comparisons within each type of HCRU or cost (all-cause, non-DMT and MS-related, and non-DMT) by controlling for the false discovery rate using the Benjamini and Hochberg 1995 method.

Table S2: All-cause and MS-related non-DMT costs by place of service

	All-cause, non-DMT costs			MS-related, non-DMT costs		
Costs during follow-up period, $[a,b]	**1L OCR cohort (N=347)**	**2L+ OCR cohort (N=347)**	**p-value[c]**	**1L OCR cohort (N=347)**	**2L+ OCR cohort (N=347)**	**p-value[c]**
Full follow-up period						
Total costs, mean (SD)	16,782 (14,048, 19,517)	28,275 (23,271, 33,280)	<0.001	8,775 (7,021, 10,528)	17,260 (13,295, 21,225)	<0.001
Outpatient	13,279 (11,040, 15,518)	18,855 (15,700, 22,010)	0.011	7,750 (6,182, 9,319)	12,317 (10,069, 14,565)	0.004
Inpatient	672 (199, 1,145)	3,169 (393, 5,946)	0.104	548 (115, 981)	2,778 (91, 5,465)	0.115
Emergency department	553 (379, 726)	982 (756, 1,209)	0.008	227 (134, 319)	533 (365, 702)	0.006
Pharmacy	2,279 (1,717, 2,841)	5,269 (3,704, 6,833)	0.002	249 (103, 396)	1,631 (483, 2,780)	0.04
Follow-up period 1						
Total costs, mean (SD)	16,784 (13,688, 19,880)	32,221 (25,073, 39,369)	<0.001	9,282 (7,116, 11,448)	20,072 (14,041, 26,104)	0.004
Outpatient	13,394 (10,860, 15,929)	20,639 (16,921, 24,358)	0.006	8,309 (6,361, 10,257)	13,747 (10,914, 16,580)	0.006
Inpatient	400 (2, 797)	3,593 (0, 8,011)	0.177	314 (0, 676)	3,286 (0, 7,656)	0.198
Emergency department	521 (302, 739)	1,059 (790, 1,328)	0.007	195 (98, 293)	513 (363, 664)	0.003
Pharmacy	2,469 (1,681, 3,257)	6,930 (3,567, 10,293)	0.024	464 (67, 860)	2,526 (44, 5,009)	0.13
Follow-up period 2						
Total costs, mean (SD)	14,687 (11,953, 17,421)	25,261 (20,055, 30,467)	0.002	6,512 (4,921, 8,103)	14,691 (10,968, 18,413)	<0.001
Outpatient	10,958 (8,783, 13,132)	18,275 (13,952, 22,598)	0.009	5,295 (4,011, 6,579)	11,833 (8,625, 15,041)	0.001
Inpatient	1,073 (145, 2,001)	1,842 (104, 3,580)	0.580	868 (53, 1,682)	1,553 (20, 3,086)	0.58
Emergency department	517 (306, 728)	931 (428, 1,434)	0.229	202 (97,307)	621 (148, 1,094)	0.171
Pharmacy	2,139 (1,402, 2,877)	4,213 (3,179, 5,248)	0.005	147 (39,255)	684 (208, 1,159)	0.073

1L = first-line; 2L+ = second- or later-line; DMT = disease-modifying therapy; MS = multiple sclerosis; OCR = ocrelizumab; SD = standard deviation.

Notes:

[a] The full follow-up period includes the period from the initiation of the first-line DMT (index date 1) to the minimum of the end of continuous eligibility for each matched pair. Follow-up period 1 includes the period from index date 1 to the date of initiation of second of later-line OCR (index date 2) among pwMS in the 2L+ OCR cohort and their matched pwMS in the 1L OCR cohort. Follow-up period 2 includes the period from index date 2 to the end of the full follow-up period.

[b] Annual all-cause and MS-related, non-DMT costs were evaluated during the full follow-up period, follow-up period 1, and follow-up period 2 and then summarized in each period using stabilized IPT weights.

[c] All p-values were adjusted for multiple comparisons within each type of HCRU or cost (all-cause, non-DMT, and MS-related, non-DMT) by controlling for the false discovery rate using the Benjamini and Hochberg method.