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Matching-Adjusted Indirect Comparison of Local Injection-Related Reactions in Ofatumumab vs Subcutaneous Ocrelizumab in Multiple Sclerosis

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KEY FINDINGS & CONCLUSIONS

- Ofatumumab and subcutaneous ocrelizumab are two injectable anti-CD20s that differ markedly in frequency and volume of injection
- Results from this study indicate that patients receiving ofatumumab have significantly lower odds of experiencing local injection-related reactions compared with patients receiving subcutaneous ocrelizumab
  - Specifically, the odds of any local injection-related reaction and three key symptoms (erythema, pain and swelling) were >90% lower with ofatumumab than with subcutaneous ocrelizumab (p<0.001)
- These findings suggest that ofatumumab may offer a more favourable safety profile than subcutaneous ocrelizumab for patients looking to minimise local injection-related reactions

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INTRODUCTION

- Ofatumumab (OMB; subcutaneous [SC] 20 mg once monthly) and SC ocrelizumab (OCR; SC 920 mg every 6 months) are CD20-directed monoclonal antibodies approved by the US Food and Drug Administration for the treatment of relapsing multiple sclerosis (MS) based on the favourable efficacy and safety profiles presented in the ASCLEPIOS I/II and OCARINA II trials, respectively
- The differing frequency and volume per SC injection between OMB and SC OCR may have implications on localised reaction risk; however, risk of local injection-related reactions (IRRs) has not been compared between OMB and SC OCR
- We present the results of an unanchored matching-adjusted indirect comparison (MAIC) of the risk of local IRRs between OMB and SC OCR

OBJECTIVE

- To compare the risk of local IRRs from the first administered dose between OMB and SC OCR in adult patients with relapsing MS (RMS)

METHODS

Study design and measurements

Overview

- An unanchored MAIC was conducted to adjust individual patient-level data (IPD) from ASCLEPIOS I/II to match aggregate baseline characteristics of the OCARINA II patient population, enabling a balanced comparison of risk of local IRRs

Data source

- This study is based on secondary use of IPD from the ASCLEPIOS I/II trials and published aggregate data from the OCARINA II trial[1,2]
- ASCLEPIOS I/II are identical phase 3 randomised, double-blind, parallel-group, multicentre clinical trials comparing OMB with teriflunomide in patients with RMS[3]
- OCARINA II is a phase 3 randomised, open-label, parallel-group, multicentre trial comparing SC OCR and intravenous OCR in patients with RMS or primary progressive MS (PPMS)[4]

Population alignment

- Eligibility and exclusion criteria from OCARINA II were applied to the IPD of ASCLEPIOS I/II, when feasible, to align the two trial populations
  - Specifically, patients treated with OMB were excluded from this analysis if they did not meet the required washout durations for prior therapies as defined by OCARINA II

Weighting procedure

- IPD from ASCLEPIOS I/II were weighted to match the reported baseline distributions of the SC OCR arm from OCARINA II
- Cohorts were balanced on all covariates reported in OCARINA II and available in ASCLEPIOS I/II (age, sex, weight, time since symptom onset, MS subtype, absence of T1 gadolinium-enhancing lesions, Expanded Disability Status Scale [EDSS] and prior disease-modifying therapy [DMT] exposure)
  - Patients in the IPD dataset with missing covariate data were excluded

Outcome definition

- Local IRRs were defined as localised symptoms occurring within 24 hours after the first SC injection
  - Three specific symptoms were assessed in this study: erythema, pain, and swelling, which were the most common local IRRs in OCARINA II
- Any local IRR refers to any local IRRs and was not limited to erythema, pain and swelling

Statistical analysis

- Patient demographic and clinical characteristics were described before and after weighting
- Odds ratios (ORs) and associated 95% confidence intervals (CIs) were estimated before and after weighting for any local IRR and each of the three symptoms
- Standard errors for OR estimates were calculated using the HC3 robust sandwich estimator, which provides conservative variance estimates when dealing with low event counts

RESULTS

Patient characteristics before and after weighting

- After applying OCARINA II exclusion criteria and removing patients with missing covariate data, 815 (86%) of the total 946 patients were retained in the OMB cohort
  - The SC OCR cohort consisted of 118 patients
- After weighting the OMB cohort, the proportions of categorical variables and means (standard deviations [SDs]) of continuous variables matched those of the SC OCR cohort (**Table 1**)

Table 1. Patient characteristics before and after weighting

	Before weighting		After weighting	
	OMB (N=815)	SC OCR (N=118)	OMB[a] (N=815)	SC OCR (N=118)
Age, mean (SD), years	38.5 (9.1)	39.9 (11.4)	39.9 (11.4)	39.9 (11.4)
Female, n (%)	547 (67.1)	77 (65.3)	532 (65.3)	77 (65.3)
Weight, mean (SD), kg	74.2 (19.3)	75.4 (16.6)	75.4 (16.6)	75.4 (16.6)
Years since symptom onset, mean (SD)	8.1 (7.1)	7.7 (8.3)	7.7 (8.3)	7.7 (8.3)
MS subtype[b], n (%)				
RRMS	766 (94.0)	105 (89.0)	725 (89.0)	105 (89.0)
SPMS or PPMS	49 (6.0)	13 (11.0)	90(11.0)	13 (11.0)
SPMS	49 (6.0)	2 (1.7)	90 (11.0)	2 (1.7)
PPMS	0 (0.0)	11 (9.3)	0 (0.0)	11 (9.3)
No T1 Gd+ lesions, n (%)	489 (60.0)	82 (69.5)	566 (69.5)	82 (69.5)
EDSS at baseline				
Median (Q1–Q3)	3.0 (2.0–4.0)	2.5 (NR–NR)	2.5 (1.5–4.0)	2.5 (NR–NR)
Range	0.0, 6.0	0.0, 6.5	0.0, 6.0	0.0, 6.5
Prior DMT exposure, n (%)	439 (53.9)	65 (55.1)	449 (55.1)	65 (55.1)

[a]Baseline characteristics after weighting were computed using scaled weights to ensure the total weighted sample size matched the unweighted sample size.
[b]Because the OMB arm had no patients with PPMS, SPMS and PPMS were combined into a single category to make reweighting feasible. Thus, the analysis included two categories for MS subtype: RRMS and SPMS or PPMS.
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; NR, not reported; OCR, ocrelizumab; OMB, ofatumumab; PPMS, primary progressive multiple sclerosis; Q, quartile; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

- In the matched OMB and SC OCR cohorts, mean (SD) age at baseline was 40 (11) years. Most (65%) patients were female, and 89% had relapsing-remitting MS compared with 11% of patients with secondary progressive MS or PPMS
- 55% of patients had prior DMT exposure, and median EDSS was 2.5, indicating mild disability

MAIC diagnostics

- After applying MAIC weights, the effective sample size of the OMB cohort was 432, representing a 47% reduction from the unweighted sample of 815. The scaled weights ranged from 0.01 to 6.87, with a median (interquartile range) of 0.71 (0.43–1.21)
- Weights were not truncated as truncation did not meaningfully affect covariate balance or impact the safety outcome results

Safety outcomes

- After balancing the OMB and SC OCR cohorts, the odds of experiencing any local IRR including erythema, pain and swelling were significantly lower in the OMB cohort than in the SC OCR cohort (**Table 2**):
  - **Any local IRR:** 97% lower odds in OMB vs. SC OCR (OR: 0.028; 95% CI: 0.013 to 0.062; p<0.001)
  - **Erythema:** 96% lower odds in OMB vs. SC OCR (OR: 0.038; 95% CI: 0.013 to 0.110; p<0.001)
  - **Pain:** 93% lower odds in OMB vs. SC OCR (OR: 0.067; 95% CI: 0.019 to 0.242; p<0.001)
  - **Swelling:** Not observed in OMB vs. 8.5% in SC OCR (OR: $1.6e^{-9}$; 95% CI: $8.0e^{-10}$ to $3.0e^{-9}$; p<0.001)

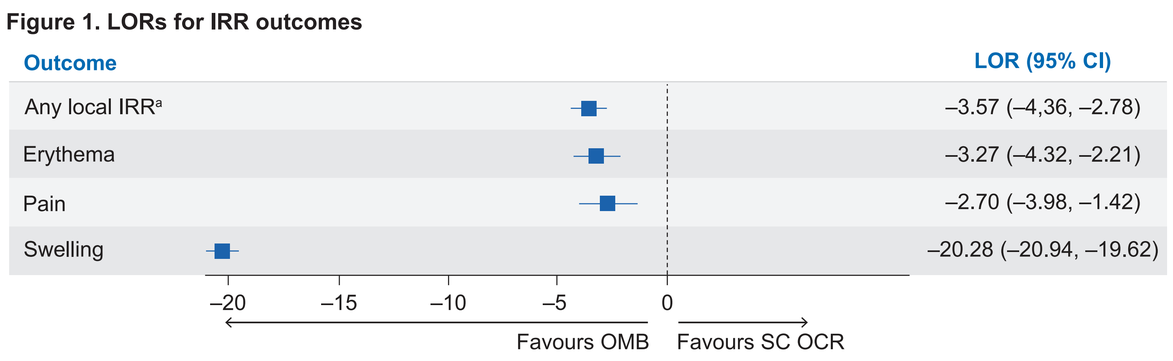
Table 2. Local IRRs before and after weighting

	Before weighting		After weighting			
	OMB (N=815)	SC OCR (N=118)	OMB[a] (N=815)	SC OCR (N=118)	OR (95% CI)[b]	p-value
Local IRRs[c], n (%)						
Any local IRR[d]	21 (2.6)	54 (45.8)	19 (2.3)	54 (45.8)	0.028 (0.013–0.062)	<0.001
Erythema	9 (1.1)	35 (29.7)	13 (1.6)	35 (29.7)	0.038 (0.013–0.110)	<0.001
Pain	9 (1.1)	17 (14.4)	9 (1.1)	17 (14.4)	0.067 (0.019–0.242)	<0.001
Swelling	0 (0.0)	10 (8.5)	0 (0.0)	10 (8.5)	$1.6e^{-9}$ ($8.0e^{-10}$–$3.0e^{-9}$)	<0.001

[a]OMB statistics after weighting were computed using scaled weights to ensure the total weighted sample size matched the unweighted sample size.
[b]Robust standard errors were calculated using the HC3 estimator, which provided conservative variance estimates when dealing with low event counts.
[c]Local IRRs presented were limited to events occurring within 24 hours of the first injection.
[d]'Any local IRR' includes all symptoms related to local IRRs and not limited to erythema, pain and swelling.
CI, confidence interval; IRR, injection-related reaction; OCR, ocrelizumab; OMB, ofatumumab; OR, odds ratio; SC, subcutaneous.

- **Figure 1** presents the log-odds ratios, highlighting the relative benefit of OMB over SC OCR across all safety outcomes

Figure 1. LORs for IRR outcomes



[a]'Any local IRR' includes all symptoms related to local IRRs and not limited to erythema, pain and swelling.
CI, confidence interval; IRR, injection-related reaction; LOR, log-odds ratio; OCR, ocrelizumab; OMB, ofatumumab; SC, subcutaneous.

Limitations

- The absence of a common comparator prevents adjustment for unmeasured confounding
- Without access to OCARINA II IPD, some population differences could not be adjusted for (eg., OCARINA II included patients ≤65 years and those with PPMS, whereas ASCLEPIOS I/II included patients ≤55 years and excluded PPMS), potentially introducing bias into the MAIC
- Data are collected from clinical trials with stringent eligibility criteria, which may limit the generalisability of the findings to real-world settings

References

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Disclosures

Ming-Hui Tai, Brandon Brown and **Abhijit Gadkari** are employees of Novartis Pharmaceuticals Corporation. **Lily Chafetz, Riley Taiji** and **Francis Vekeman** are employees of STATLOG Inc., which has received funding from Novartis Pharmaceuticals Corporation. **Lisa Leung** is a former employee of STATLOG Inc.