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Immunoglobulin Level Changes in Patients With Multiple Sclerosis Treated With Anti-CD20 Monoclonal Antibodies

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KEY FINDINGS & CONCLUSIONS

- The findings of this retrospective cohort study suggest a small reduction in immunoglobulin G (IgG) and immunoglobulin M (IgM) values over time on the B-cell–depletion therapies ocrelizumab (OCR), rituximab (RTX), and ofatumumab (OMB)
- Of patients treated with OCR and RTX, few had IgG levels <500 mg/dL and IgM levels <25 mg/dL. Of patients treated with OMB, none had IgG <500 mg/dL and few had IgM <25 mg/dL
- The OMB cohort size was much smaller and the treatment duration much shorter than for the OCR and RTX cohorts; therefore, additional follow-up is needed to assess comparisons between therapies

INTRODUCTION

- Ocrelizumab (OCR), rituximab (RTX), and ofatumumab (OMB) are B-cell–depleting antibodies used in the treatment of multiple sclerosis (MS). Although OCR and OMB are approved for the treatment of relapsing forms of MS (RMS), RTX is used off label[1-3]
- A decrease in immunoglobulin G (IgG) serum concentration has been associated with the depletion of B cells, which may pose an increased risk of infection[4]

OBJECTIVE

- The objective of this study was to examine IgG and immunoglobulin M (IgM) levels over time in patients with MS initiating an anti-CD20 therapy

METHODS

Study Design

- This was a retrospective, observational cohort study that utilized data collected from electronic medical records (EMRs) and patient charts from the Health Data Compass platform at the Rocky Mountain MS Center at the University of Colorado
  - Compass is a health data warehouse at the University of Colorado that integrates EMR patient data, billing data, and a variety of state data sources, including all-payer claims databases

Study Endpoints

- Inclusion criteria:
  - Aged ≥18 years at the time of MS diagnosis
  - A diagnosis of RMS (including clinically isolated syndrome, relapsing-remitting MS, and secondary progressive MS)
  - Newly initiated treatment with OCR, RTX, or OMB after March 2017
  - Naïve to anti-CD20 therapies at the time of initiation of OCR, RTX, or OMB
  - ≥1 IgG lab value before and after initiating therapy with OCR, RTX, or OMB
- Patients who had participated in a clinical trial were excluded

Statistical Outcomes

- IgG and IgM levels were evaluated over time in patients with MS receiving OCR, RTX, or OMB

Statistical Analysis

- Demographic and disease history variables were examined using summary statistics
- IgG and IgM levels were analyzed using longitudinal regression (repeated measures model) on the logarithmic scale to assess if changes over time were statistically significant
  - Different models were fit for each disease-modifying therapy, and the models utilized a continuous time first order autoregression repeated measures covariance structure
- No covariate adjustments were made in these analyses

RESULTS

Patient Demographics and Clinical Characteristics

- A total of 118 patients received OCR, 140 patients received RTX, and 68 patients received OMB (**Table 1**)
- Mean age was similar across cohorts, but OMB patients were slightly younger
- Across all cohorts, the majority of patients were female, with the greatest percentage of female patients in the OMB cohort
- OMB patients had the lowest mean duration from disease onset and lowest mean duration from disease diagnosis

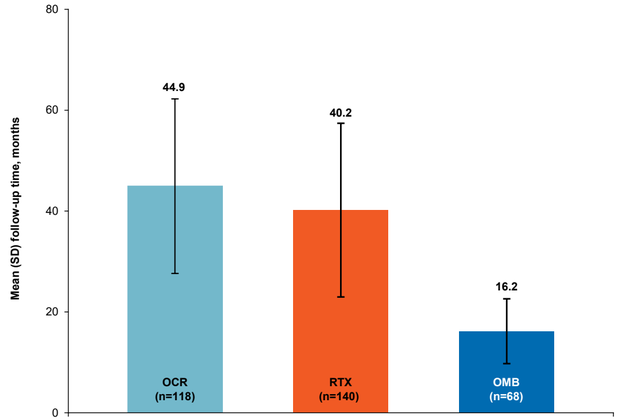
Table 1. Baseline Patient Characteristics

	OCR (n=118)	RTX (n=140)	OMB (n=68)
Age, mean (SD), y	42.81 (10.84)	42.92 (13.03)	40.74 (10.14)
Female, n (%)	82 (69.49)	96 (68.57)	55 (80.88)
Race, n (%)			
White	99 (83.90)	100 (71.43)	53 (81.54)
Black	4 (3.39)	19 (13.57)	3 (4.62)
Asian	0	0	0
Other Asian	0	2 (1.43)	2 (3.08)
Native American or Pacific Islander	0	0	0
Other	11 (9.32)	15 (10.71)	4 (6.15)
>1 race	0	1 (0.71)	2 (3.08)
Unknown	4 (3.39)	3 (2.14)	1 (1.54)
Missing	0	0	3
Ethnicity, n (%)			
Non-Hispanic	108 (91.53)	115 (82.14)	62 (91.18)
Hispanic	9 (7.63)	20 (14.29)	6 (8.82)
Unknown	1 (0.85)	4 (2.86)	0
Patient unable to answer	0	1 (0.71)	0
Type of MS, n (%)			
RRMS	97 (82.20)	98 (70.00)	64 (94.12)
SPMS	12 (10.17)	29 (20.71)	3 (4.41)
PPMS	9 (7.63)	13 (9.29)	1 (1.47)
Mean (SD) duration from disease onset, y	10.87 (9.46)	9.04 (9.35)	7.38 (7.87)
Mean (SD) duration from disease diagnosis, y	7.53 (7.91)	6.17 (8.54)	4.03 (6.37)
Mean (SD) number of previous DMTs	1.50 (1.47)	1.11 (1.50)	1.08 (1.48)
Previous DMT, n (%)			
Interferons	9 (7.63)	14 (10.00)	0
Glatiramer acetate	16 (13.56)	13 (9.29)	4 (5.88)
Natalizumab	7 (5.93)	14 (10.00)	6 (8.82)
Fingolimod	16 (13.56)	12 (8.57)	7 (10.29)
Dimethyl fumarate	25 (21.19)	14 (10.00)	9 (13.24)
Other	8 (6.78)	5 (3.57)	5 (7.35)
None	37 (31.36)	68 (48.57)	37 (54.41)
Median (IQR) time on previous DMT, months	38.60 (14.13, 72.93)	28.45 (12.17, 62.77)	26.33 (7.27, 66.47)
Median (IQR) time since previous DMT, months	0.63 (0.23, 7.20)	1.65 (0.48, 12.32)	1.00 (0.00, 2.47)

DMT, disease-modifying therapy; IQR, interquartile range; MS, multiple sclerosis; OCR, ocrelizumab; OMB, ofatumumab; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; RTX, rituximab; SPMS, secondary progressive multiple sclerosis

- Among all cohorts, patients receiving OMB had the shortest mean time on therapy (**Figure 1**), which is expected because OMB was approved in 2020
- The mean (SD) number of infusions for patients treated with OCR and RTX was 6.70 (2.81) and 6.16 (2.84), respectively

Figure 1. Follow-Up Time for Patients Treated With OCR, RTX, or OMB



OCR, ocrelizumab; OMB, ofatumumab; RTX, rituximab

Baseline IgG and IgM Levels

- Baseline IgG and IgM levels were within normal reference ranges across all 3 cohorts (**Table 2**)

Table 2. Baseline IgG and IgM Values for Patients With MS Initiating OCR, RTX, or OMB

	OCR (n=118)	RTX (n=140)	OMB (n=68)
IgG, geometric mean (95% CI)*	957.71 (922.24-994.54)	940.34 (901.80-980.53)	978.56 (912.07-1049.90)
IgM, geometric mean (95% CI)*	101.90 (92.32-112.47)	101.11 (91.68-111.51)	104.01 (89.58-120.77)

IgG, immunoglobulin G; IgM, immunoglobulin M; MS, multiple sclerosis; OCR, ocrelizumab; OMB, ofatumumab; RTX, rituximab
*Calculated using all available baseline lab values with 12 months prior to OCR, RTX, or OMB therapy

Annual Changes in IgG and IgM Levels

- Across all cohorts, IgG levels demonstrated small decreases over time (**Table 3**)
- Statistically significant decreases in IgG were observed for OCR and RTX, with decreases of 2.93% per year and 1.81% per year, respectively. For OMB, a decrease of 2.63% per year was observed, but this did not reach statistical significance
- All anti-CD20 therapies demonstrated statistically significant percentage decreases per year in IgM

Table 3. Percentage Decrease per Year in IgG and IgM Levels in Patients Receiving OMB, OCR, or RTX

DMT	Ig	% change per year	95% CI	p-value
OCR (n=118)	IgG	-2.93	-4.30, -1.55	<0.0001
	IgM	-17.82	-20.34, -15.23	<0.0001
RTX (n=140)	IgG	-1.81	-2.88, -0.73	0.0011
	IgM	-19.00	-21.42, -16.52	<0.0001
OMB (n=68)	IgG	-2.63	-7.27, 2.24	0.2829
	IgM	-27.90	-35.02, -20.00	<0.0001

DMT, disease-modifying therapy; Ig, immunoglobulin; IgG, immunoglobulin G; IgM, immunoglobulin M; OCR, ocrelizumab; OMB, ofatumumab; RTX, rituximab
Note: The model for RTX-IgG had difficulties fitting the longitudinal covariance structure

Percentage of Patients With Low Ig Values

- Among the 3 cohorts, the OMB cohort had no patients with IgG levels <500 mg/dL and a low percentage of patients with ≥1 lab IgM value of <25 mg/dL (**Table 4**)

Table 4. Percentage of Patients With Low Ig Values*

	OCR		RTX		OMB	
	% (n/N)	95% CI	% (n/N)	95% CI	% (n/N)	95% CI
IgG <500 mg/dL	5.93 (7/118)	2.42-11.84	5.71 (8/140)	2.50-10.95	0 (0/68)	0.00-5.28
IgM <25 mg/dL	15.38 (18/117)	8.85-21.92	10.95 (15/137)	5.72-16.18	6.25 (4/64)	1.73-15.24

Ig, immunoglobulin; IgG, immunoglobulin G; IgM, immunoglobulin M; OCR, ocrelizumab; OMB, ofatumumab; RTX, rituximab
*Defined as ≥1 IgG lab value of <500 mg/dL or ≥1 IgM lab value of <25 mg/dL

LIMITATIONS

- The number of patients in the OMB cohort was much smaller than the number of patients in the OCR and RTX cohorts and they were followed for a much shorter period of time, thus limiting the interpretation of these results
- This was a descriptive study and no covariate adjustments were made in these analyses

FUTURE DIRECTIONS

- Additional follow-up is being collected to assess comparisons between therapies
- Clinical predictors of IgG and IgM baseline levels and their rates of change over time will be examined

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Disclosures

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