ACAPELLA: B-cell Reconstitution in Ocrelizumab-Treated Patients, 2021 Update

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Background

Ocrelizumab (OCR) is a humanized monoclonal antibody targeting CD20+ B-cells, approved for the treatment of relapsing (RMS) and primary progressive multiple sclerosis (PPMS). The timing of B-cell repletion and the relationship between disease breakthrough and MS is unclear. The PI states that "B-cell counts rose to above the lower limit of normal (LLN) or above baseline counts between infusions of OCR at least one time in 0.3% to 4.1% of patients. The median time for B-cell counts to return was 72 weeks (range 27-175 weeks)".[1] Real world data on the incidence and degree of B-cell repletion with ocrelizumab is limited.

Objectives

As part of the ACAPELLA trial (a prospective study assessing OCR-associated adverse events in a real-world population) we sought to describe the incidence and degree of B-cell repletion in our patients treated with OCR and to evaluate any correlation between CD19+ cell count, demographics, AEs, and breakthrough disease.

Methods

This study included 294 patients, a sub-group of the ACAPELLA trial (all consenting subjects receiving commercial OCR at The Elliot Lewis Center since its approval in March 2017) who had at least 2 cycles of OCR. CD19+ cell counts were obtained as a part of standard pre-infusion laboratory assessments. We defined 4 groups: non-repleters with 0 - 9 cells/µL, mild repleters with 10 - 49 cells/uL, moderate repleters with 50 - 79 cells/µL, and marked repleters ≥80 cells/µL (local laboratory range 110-660 cells/µL). Subjects were assigned to these subgroups based on their highest CD19 value at any cycle. Subjects were monitored for occurrence of breakthrough disease and other AEs. This dataset reflects results collected through September 1, 2021.

Results

- 31.0% (91/294) of the study population showed some degree of repletion at one or more time point.
- 8 patients fully repleted with values from 114-319 cells/µL. Time from last infusion ranged from 23-34 weeks in this subgroup.
- After 2 cycles of OCR, 27% of patients were mild repleters and 8% were moderate or marked repleters.
- With additional cycles of OCR, a greater proportion of patients became non-repleters.
- Moderate or marked repleters tended to remain repleters with subsequent infusions.
- There was no correlation between B-cell repletion and age, sex, or prior immunosuppression.
- There was an association between increasing BMI and B-cell repletion ($p<0.0001$).
- Repletion was not correlated with MRI breakthrough or clinical relapse in our dataset.

Figure 1. CD19 Distribution by OCR Cycle

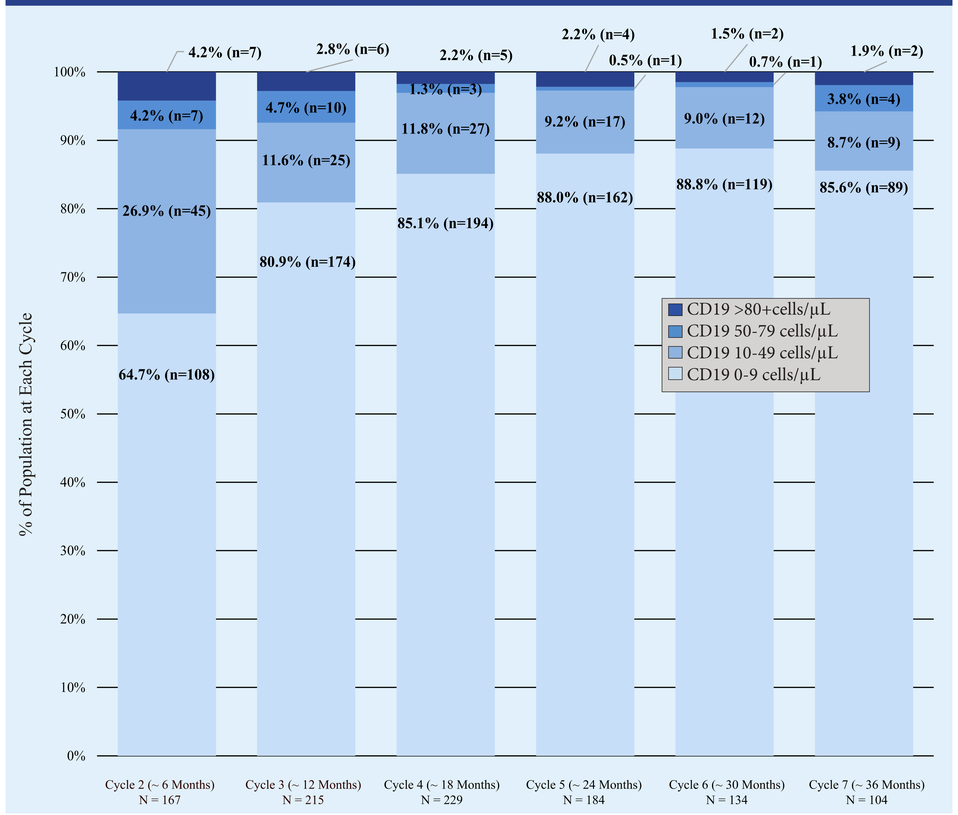

Table 1. CD19 Repletion: Patient Characteristics and Occurrence of Breakthrough Disease

	Total Population	CD19 (0 - 9 cells/µL)	CD19 (10 - 49 cells/µL)	CD19 (50 - 79 cells/µL)	CD19 (80+ cells/µL)
# of Patients	294	203 (69%)	64 (22%)	13 (4%)	14 (5%)
Median Age (Range)	51 (18 - 70)	52 (21 - 70)	48 (18 - 68)	51 (31 - 68)	47 (24 - 56)
% Female	71%	71%	73%	77%	57%
Mean EDSS	3.4	3.5	3.0	3.4	2.7
Mean BMI	28.1	27.0	29.4	34.1	32.6
Prior Immunosupressive Tx*	26	16	8	1	1**
Disease Breakthrough	12	8	3	---	1
Clinical Relapse w/ MRI Activity	6	4	2	---	0
Clinical Relapse w/o MRI Activity	3	2	1	---	0
MRI Relapse w/o Clinical Activity	3	2	0	---	1

*Including cyclophosphamide, cellcept, novantrone, cytoxan, adriamycin, methotrexate, azathioprine, and basiliximab.
** For treatment of breast cancer.

Conclusions

In this sub-study of the ACAPELLA cohort, we characterized B-cell repletion and the relationship between repletion and disease breakthrough.

Mild B-cell repleters (10 - 49 cells/µL) were seen in 26.9% of patients after two cycles of OCR, but with additional cycles a greater proportion of patients became non-repleters (0 - 9 cells/µL). This suggests that increasing exposure to OCR may lead to cumulative suppression of B-cell recovery.

While the number of moderate or marked repleters (≥50 cells/µL) in our study was small, they had a tendency to remain repleters over time.

Repletion was more common in patients with a higher BMI. Though our data do not show an association between CD19 repletion and efficacy, it may be that patients with higher BMI are at greater risk for clinical or radiographic breakthrough.

While CD19 repletion may correlate with disease breakthrough in other autoimmune conditions2,3, its role in OCR-treated MS patients is less clear. In our study, there was no correlation between disease breakthrough and B-cell repletion, suggesting that it does not necessarily herald clinical or radiographic relapse.

References

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3. Damato V, Evoli A, Iorio R. Efficacy and Safety of Rituximab Therapy in Neuromyelitis Optica Spectrum Disorders: A Systematic Review and Meta-analysis. JAMA Neurol. 2016;73(11):1342–1348.