# ACAPELLA: Hypogammaglobulinemia in Ocrelizumab Treated Patients, 7 Year Data

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## Background

Ocrelizumab (OCR) is a humanized monoclonal anti-CD20 antibody approved for treatment of relapsing (RMS) and primary progressive multiple sclerosis (PPMS). Prolonged treatment with anti B-cell therapy is known to be associated with a risk of hypogammaglobulinemia[1] and the potential for increased infection risk. This is of particular concern in older patients with chronic B-cell depletion, in whom immunosenescence may pose an additional risk for infection.

During the phase III trials for OCR, a small proportion of patients developed low IgG (1.5% in OPERA I & II and 1.1% in ORATORIO) after 2-3 years of OCR treatment, but this was not associated with a higher rate of infection[2,3]. Patients with preexisting low IgG were excluded from the trials.

## Objectives

As part of the ACAPELLA trial (a prospective study assessing OCR-associated adverse events in a real-world population), we evaluated the impact of OCR on IgG levels. This dataset reflects results collected through March 1, 2024.

## Methods

This study includes (449) patients receiving commercial OCR at The Elliot Lewis Center of whom 434 patients had baseline IgG levels. Normal IgG was defined as 600-1640 mg/dL.

Subjects were monitored for infections and serious adverse events (SAEs). Subjects had biannual assessments of serum IgG. Cycle 1 includes two 300 mg doses of OCR, Cycle 2 is the first full 600 mg dose.

## Results

**Table 1: IgG Values by OCR Cycle**

| | Baseline | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | Cycle 7 | Cycle 8 | Cycle 9 | Cycle 10 | Cycle 11 | Cycle 12 | Cycle 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N | 449 | 350 | 307 | 263 | 233 | 205 | 179 | 153 | 119 | 91 | 62 | 37 |
| Mean IgG Value (mg/dL) | 1013 | 1001 | 1001 | 991 | 970 | 941 | 920 | 916 | 904 | 929 | 889 | 900 |
| % Change From BL | | -1.25 | -1.22 | -2.17 | -4.28 | -7.14 | -9.23 | -9.55 | -10.76 | -8.30 | -12.27 | -11.22 |
| Absolute Change from BL, Mean | | -12.62 | -12.35 | -22.01 | -43.31 | -72.37 | -93.51 | -96.74 | -108.97 | -84.08 | -124.34 | -114 |
| Below LLN (600 mg/dL) %(N) | 3%(15) | 4%(13) | 4%(12) | 5%(13) | 6%(14) | 6%(13) | 10%(18) | 9%(14) | 8%(10) | 4%(4) | 11%(7) | 8%(3) |

**Figure 1: Percent Change in IgG Values from Baseline by Cycle**

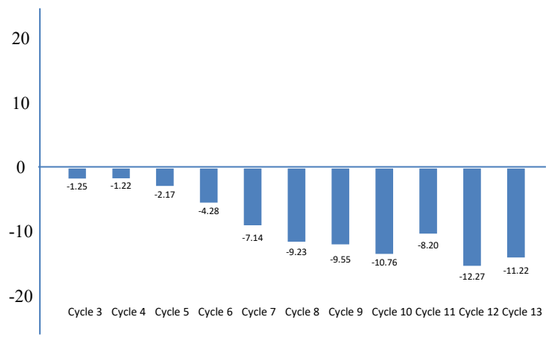



**Figure 2: Patients with at Least One Occurrence of Low IgG (<600mg/dL) N=42**

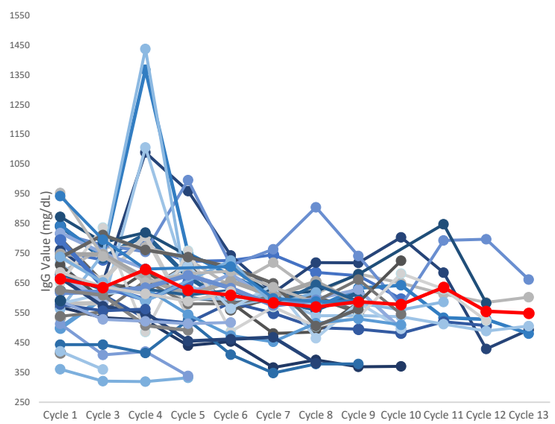
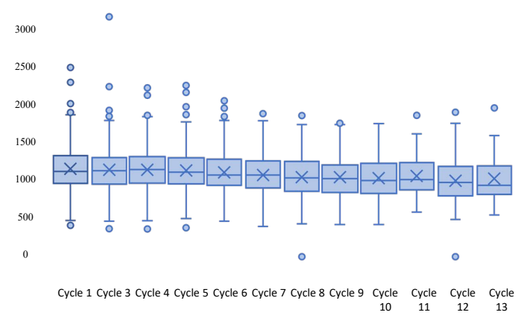



**Figure 3: IgG Values by Cycle**




**Over the course of 13 OCR treatment cycles:**

- Mean IgG declined by 11.22%.
- Ninety-two percent of patients had IgG that remained above the lower limit of normal.
- A small proportion of patients developed hypogammaglobulinemia (Table 1). Four patients received IVIG treatment.
- 15 patients who had low IgG values at baseline (<600 mg/dL) had an infection rate of 63.74 cases per 100 patient years (PY) (48.57 cases per 100PY excluding COVID-19).
- Patients with normal IgG at baseline had an infection rate of 67.65 cases per 100PY (48.57 cases per 100PY excluding COVID-19).

## Summary

- In patients completing up to 13 OCR cycles, a downward trend in IgG levels was observed over the first 10 cycles but then leveled off.
- Although the number of patients with low IgG at baseline are too small to make definitive conclusions, they did not have an increased risk of infection compared to our population with normal baseline IgG or compared to the 5-year clinical trial population (76.2 PY).[5]

**References:**

1. Marcinnò A, Marnetto F, Valentino P et al. Rituximab-induced Hypogammaglobulinemia in Patients with Neuromyelitis Optica Spectrum Disorders. Neurology Neuroimmunology & Neuroinflammation, 2018 Nov 5, 5(6): e498
2. Montalban X, Hauser SL, Kappos L et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. New England Journal of Medicine, 2017 Jan 19; 376:209-220
3. Hauser SL, Bar-Or A, Comi G et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. New England Journal of Medicine, 2017 Jan 19; 376:221-234
4. Baber U, Bouley A, Egnor E, Sloane JA. Anti-JC virus antibody index changes in rituximab-treated multiple sclerosis patients. J Neurol. 2018 Oct; 265(10): 2342-2345.
5. Hauser SL, Kappos L, Montalban, X et al. Safety of Ocrelizumab in Patients with Relapsing and Primary Progressive Multiple Sclerosis. Neurology, 2021 Oct 19; 97(16)