ACAPELLA: Hypogammaglobulinemia and JCV Status in Ocrelizumab-Treated Patients, 2022 Update

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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). Long term exposure to other B-cell depleting agents has been associated with low immunoglobulin G (IgG) and might occur with OCR[1]. During the phase III trials for OCR, patients with preexisting low IgG were excluded. After 2-3 years of OCR treatment, a small proportion of patients developed low IgG (1.5% in OPERA I & II and 1.1% in ORATORIO), but this was not associated with a higher rate of infection[2,3].

JCV index values were not studied in the phase III trials, and the impact of long-term B-cell depletion on JCV index is uncertain[4]. A drop in IgG could lower JCV index values, possibly affecting the predictive value of the JCV index.

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 and JCV index. This dataset reflects results collected through September 1, 2022.

Methods

This study includes 429 patients receiving commercial OCR at The Elliot Lewis Center of whom 389 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 and JCV index.
Cycle 1 includes two 300 mg doses of OCR, cycle 2 is the first full 600 mg dose.

Results

Table 1: IgG Values and Change from Baseline (BL) by OCR Cycle

	Baseline N= 389	Cycle 3 N= 290	Cycle 4 N= 265	Cycle 5 N= 232	Cycle 6 N= 204	Cycle 7 N=155	Cycle 8 N= 118	Cycle 9 N= 90	Cycle 10 N= 49	Cycle 11 N=16
Mean IgG Value (mg/dL)	981	991	995	971	939	903	868	869	868	828
% Change From BL		-0.84	-0.37	-2.07	-4.64	-8.93	-12.01	-10.96	-10.10	-7.59
Mean Absolute Change From BL (mg/dL)		-8.46	-3.79	-20.98	-46.95	-90.28	-121.42	-110.85	-102.16	-76.70
Number Below LLN (%)	15 (3.9%)	13 (4.5%)	10 (3.8%)	11 (4.7%)	14 (6.9%)	10 (6.5%)	12 (10.2%)	9 (10.0%)	4 (8.2%)	0(0%)

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= 35

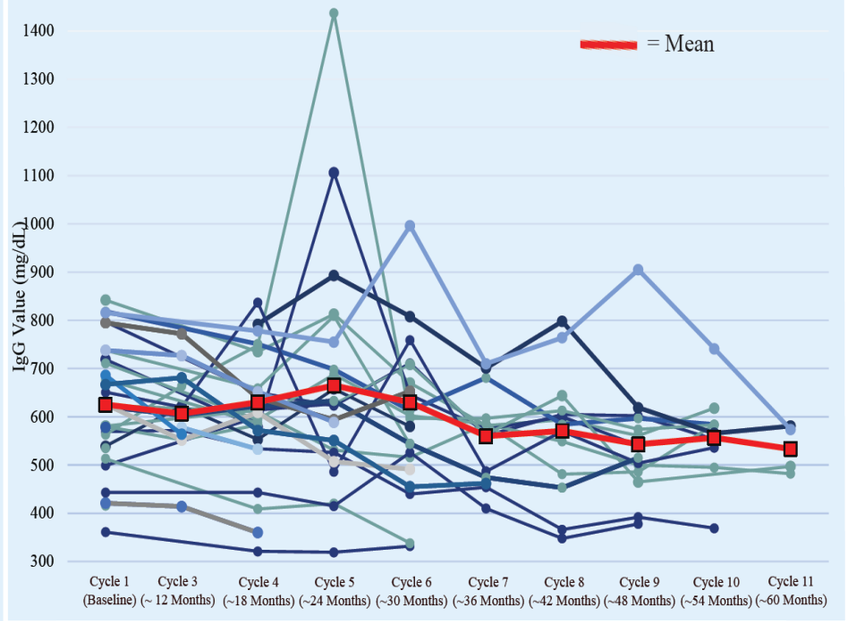
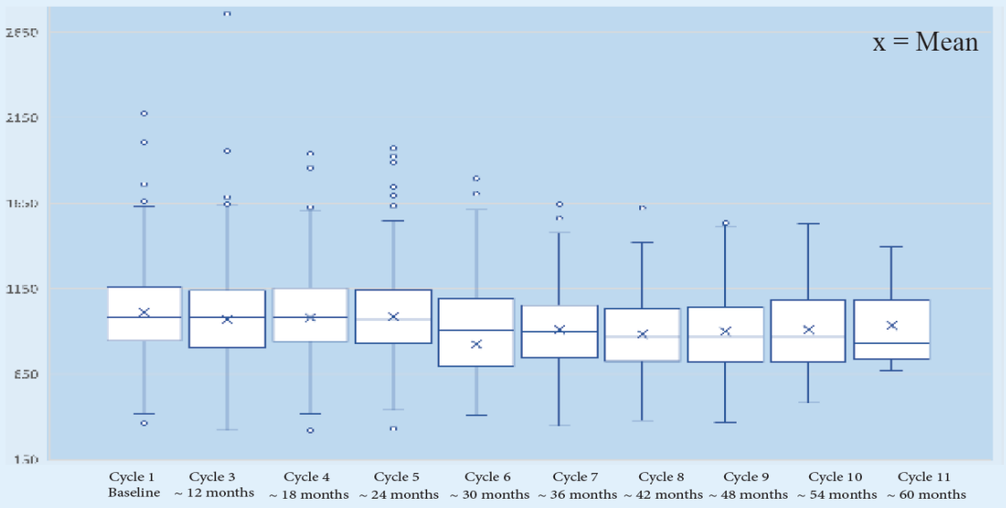


Figure 3: IgG Values by Cycle



Results Summary

- Over the course of 10 OCR treatments, mean IgG declined by10.1 %.
- Over the course of 10 OCR treatments, 91.8% of patients had IgG that remained above the lower limit of normal (>600 mg/dL).
- The 15 patients (3.9%) who had low IgG values at baseline (<600 mg/dL) had an infection rate of 55.3 per 100 PY (including COVID-19), compared with patients with normal IgG at baseline (48.9 per 100 PY).

Discussion

- Prolonged treatment with anti B-cell therapy is known to be associated with a risk of hypogammaglobulinemia 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.
- In patients completing up to 11 OCR cycles, a downward trend in IgG levels was observed. Although IgG dropped by 12% by cycle 8, 90% of patients had IgG that remained above the LLN.
- Patients with low IgG at baseline treated for up to 5 years did not have an increased rate of infection compared to the 5-year clinical trial data[5] but had a slightly higher rate of infection than our population with normal IgG at baseline.
- A drop in JCV index has been reported with rituximab[4], but the impact of OCR on JCV index is not well described. Thirty-five of 327 patients had a drop in JCV index of ≥ 0.5, and this was not associated with a decline in IgG levels. A decline in JCV index in this context may not relate to a reduction in PML risk, but this has not been studied.

Conclusions

- Patients with low baseline IgG (<600 mg/dl) remained low throughout treatment (Figure 2).
- Over the course of 11 OCR treatment cycles, IgG decreased but remained in the normal range in most patients. However, an increasing but small proportion of patients developed hypogammaglobulinemia over time (Table 1).

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)