ACAPELLA: Hypogammaglobulinemia in Ocrelizumab-Treated Patients, 6 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). Long term exposure to other B-cell depleting agents has been associated with low immunoglobulin G (IgG) and would be expected to 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].

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, 2023.

Methods

This study includes 413 patients receiving commercial OCR at The Elliot Lewis Center who 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.

Cycle 12 data were not included in data analysis due to low subject number.

Results

Table 1: IgG Values by OCR Cycle

	Baseline N= 413	Cycle 3 N= 316	Cycle 4 N= 280	Cycle 5 N= 248	Cycle 6 N= 218	Cycle 7 N=185	Cycle 8 N= 146	Cycle 9 N= 112	Cycle 10 N= 79	Cycle 11 N=43	Cycle 12 N=12
Mean IgG Value (mg/dL)	1010	1005	1005	989	966	937	894	899	892	897	918
% Change From BL		-0.52	-0.48	-2.06	-4.37	-7.26	-11.46	-11.02	-11.71	-11.16	-9.09
Absolute Change From BL, Mean		-5.28	-4.82	-20.79	-44.17	-73.31	-115.73	-111.28	-118.30	-112.75	-91.83
Below LLN (600 mg/dL) N, (%)	15 (3.6%)	13 (4.1%)	11 (3.9%)	11 (4.4%)	15 (6.9%)	11 (5.9%)	15 (10.3%)	10 (8.9%)	9 (11.4%)	4 (9.3%)	0(0%)

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

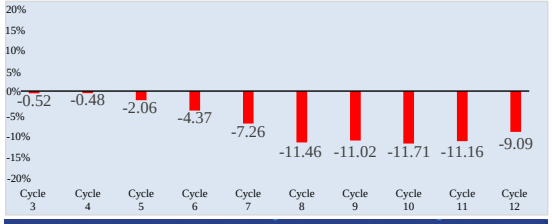


Figure 2: Patients with at Least One Occurrence of Low IgG (<600mg/dL) N= 38

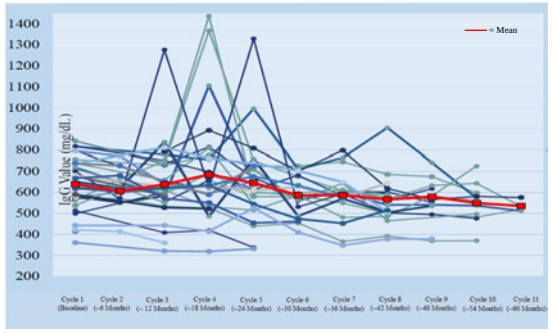
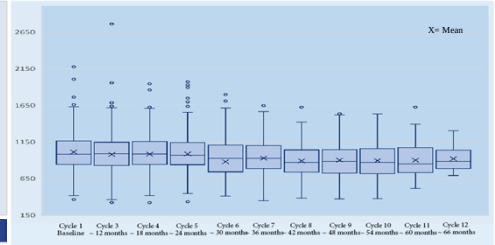


Figure 3: IgG Values by Cycle



Results Summary

During OCR treatment, mean IgG levels fell by 11.5% by 8 cycles and then leveled off without further decline through Cycle 11.

Over the course of 11 OCR treatments, 90.7% of patients had IgG that remained above the lower limit of normal (>600 mg/dL).

The 15 patients (3.6%) who had low IgG values at baseline (<600 mg/dL) had an infection rate of 48 per 100 PY, compared with 45.7 PY in patients with normal IgG at baseline (includes COVID-19 infections).

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 over the first 8 cycles but then leveled off. By cycle 11, greater than 90% of patients had IgG that remained above the LLN.

Although the number of patients with low IgG at baseline are too small to make definitive conclusions, these patients had a slightly higher rate of infection than our patients with normal IgG at baseline but did not have an increased rate of infection compared to the 5-year clinical trial data.[5]

Conclusions

Over the course of 12 OCR treatment Cycles:

- IgG decreased by roughly 10% by cycle 8 and then leveled off.
- IgG remained in the normal range in most patients.
- A small proportion of patients developed hypogammaglobulinemia (Table 1).

References:

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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)