Hypogammaglobulinemia in Ocrelizumab Treated Patients, 8 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 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 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, 2025.

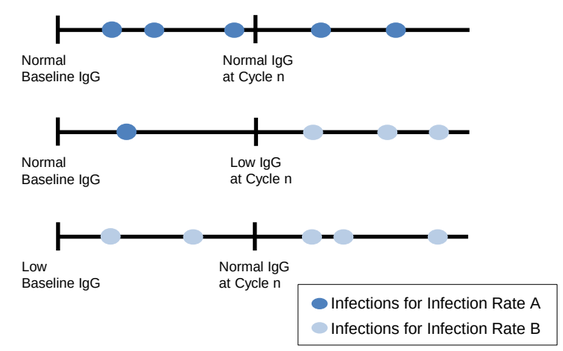
Methods

This study includes 467 patients receiving commercial OCR at The Elliot Lewis Center who had baseline IgG levels.

Patients were monitored for infections and serious adverse events (SAEs). Patients had biannual assessments of serum IgG. Cycle 1 includes two 300 mg doses of OCR and Cycle 2 is the first full 600 mg dose. Normal IgG was defined as 600-1640 mg/dL.

We calculated two infection rates for the purpose of identifying the risk of infection after the development of low IgG. Infection Rate A in patients with normal IgG values (and prior to the development of the first low IgG value); Infection Rate B in patients following any low IgG value (Figure 1).

Figure 1: Infections Used in Calculation of Infection Rates A and B



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	Cycle 14	Cycle 15
N	467	385	353	312	273	229	203	184	161	135	102	80	54	30
Mean IgG Value (mg/dL)	1019	1000	1001	977	968	942	926	921	916	924	908	896	856	840
% Change From BL		-1.9	-1.7	-4.2	-5.0	-7.6	-9.1	-9.6	-10.1	-9.3	-11.0	-12.0	-16.0	-17.6
Absolute Change from BL, Mean		-19.6	-17.8	-42.5	-51.1	-77.6	-92.9	-98.0	-103.4	-94.9	-111.6	-122.7	-162.6	-179.4
Below LLN (600 mg/dL) %(N)	3.2%(15)	4.2%(16)	3.4%(12)	4.5%(14)	5.1%(14)	6.1%(14)	9.4%(19)	8.7%(16)	8.7%(14)	7.4%(10)	8.8%(9)	8.8%(7)	11.1%(6)	10.0%(3)

Figure 2: IgG Values by Cycle

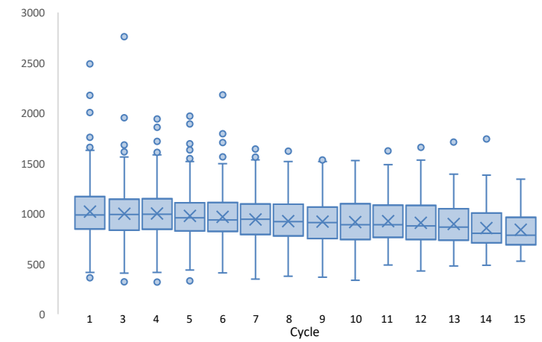
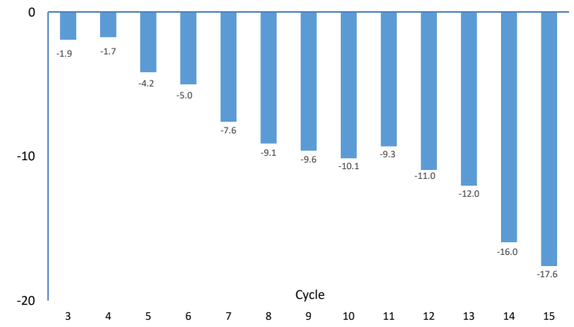


Figure 3: Percent Change in IgG Values from Baseline by Cycle



Over the course of 15 OCR treatment cycles:

- Mean IgG declined up to 17.6%.
- 10.3% of patients developed hypogammaglobulinemia (Table 1).
- Infection Rate A was 74.8 cases per 100PY, with a severe infection rate of 2.3 cases per 100PY.
- Infection Rate B was 124.6 cases per 100PY, with a severe infection rate of 5.1 cases per 100PY.
- 15 patients had low IgG values at baseline and had an infection rate of 91.5 cases per 100PY and a severe infection rate of 8.3 cases per 100PY.

Table 2: Totals Used to Calculate Infection Rates A and B

	Patient Years	Total Infections	Infection Rate (per 100PY)	Total Severe Infections	Severe Infection Rate (per 100PY)
A	1606.8	1202	74.8	37	2.3
B	118.0	147	124.6	6	5.1

**5-year combined ocrelizumab clinical trial population had an infection rate of 76.2 per 100PY.[5]*

Summary

- There was a downward trend in IgG levels in patients completing up to 15 OCR cycles.
- An increased rate of both general infections and severe infections occurred after the first instance of a low IgG value.

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)