ACAPELLA: Hypogammaglobulinemia and JCV Status in Ocrelizumab-Treated Patients, 5-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 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 March 1, 2022.

Methods

This study includes 375 patients receiving commercial OCR at The Elliot Lewis Center of whom 358 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 by OCR Cycle

	Cycle 2 N= 182	Cycle 3 N= 260	Cycle 4 N= 232	Cycle 5 N= 197	Cycle 6 N= 157	Cycle 7 N=101	Cycle 8 N= 94	Cycle 9 N= 52	Cycle 10 N= 15
IgG Value, Median (IQR) mg/dL	1050, 292	991, 319	995, 324	963, 315	929, 307	892, 283	860, 308	849, 289	858, 378
% Change From BL	3.35	-0.46	-0.20	-1.87	-5.27	-8.73	-11.83	-12.84	-5.10
Absolute Change From BL, Mean	33.9	-4.69	-2.02	-18.94	-53.39	-88.42	-119.81	-129.94	-51.58
Below LLN (600 mg/dL), N %	8 (4.4%)	12 (4.6%)	10 (4.3%)	10 (5.1%)	13 (8.3%)	8 (7.9%)	10 (10.6%)	5 (9.6%)	0 (0%)

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

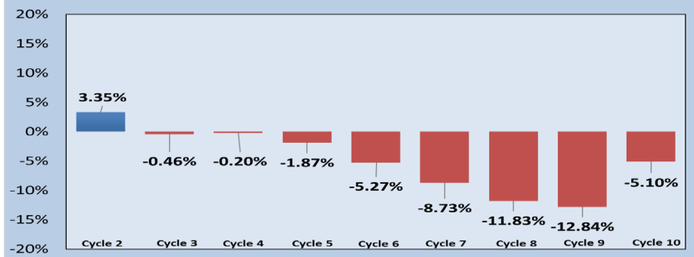


Figure 2: Patients with at Least One Occurrence of Low IgG (<600mg/dL) N= 35

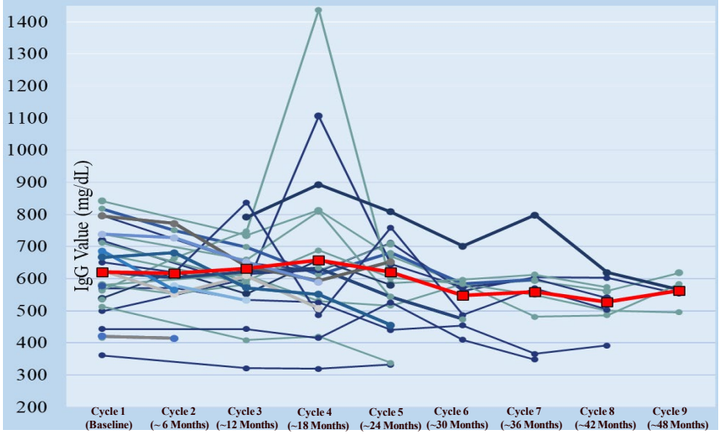
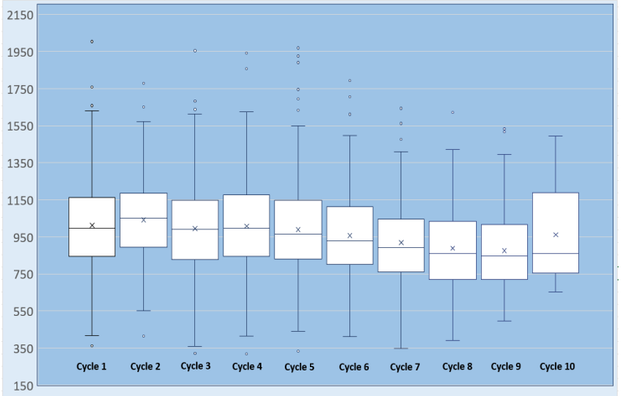


Figure 3: IgG Values by OCR Cycle



Results Summary

- Over the course of 9 OCR treatments, mean IgG declined by 12.8%.
- Over the course of 9 OCR treatments, 90.4% of patients had IgG that remained in the normal range (>600 mg/dL).
- Fifteen patients (4.2%) had low IgG values at baseline (<600 mg/dL) and an infection rate of 58.7 per 100py (including COVID-19), comparable to patients with normal IgG at baseline (58.3 per 100py).

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 those with chronic B-cell depletion, in whom immunosenescence may pose an additional risk for infection.

In patients completing up to 10 OCR cycles, a downward trend in IgG levels was observed. Although nearly 50% of patients had at least a 10% drop in IgG values by cycle 8, the majority had IgG that remained above the LLN.

Patients with low IgG treated for up to 5 years did not have an increased rate of infection compared to the 5-year clinical trial data.[5] However, over a longer period of time, it is possible that a further drop in IgG and/or a higher risk of infection may be seen.

A drop in JCV index has been reported with rituximab[4], but the impact of OCR on JCV index is not well described. Thirty-two of 354 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.

Conclusion

- Patients with low baseline IgG (<600 mg/dl) remained low throughout treatment (Figure 2) and did not have a higher rate of infection.
- An increasing proportion of patients developed hypogammaglobulinemia over time (Table 1).
- Over the course of 10 OCR treatment cycles, IgG decreased but remained in the normal range in most patients and did not result in an increased rate of infection.

References

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