ACAPELLA: Hypogammaglobulinemia and JCV Status in Ocrelizumab-Treated Patients, 2021 Update

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Background

Ocrelizumab (OCR) is a humanized monoclonal anti-CD20 antibody approved for treatment of both 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 greater risk of infection[2].

JCV index values were not studied in the phase III trials and the impact of long-term B-cell suppression on IgG levels and JCV titers is uncertain. A drop in IgG could lower JCV IgG antibody levels, possibly affecting the predictive value of JCV index invalid.

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 titers as well as any correlation between IgG levels and infection risk. This dataset reflects results collected through September 1, 2021.

Methods

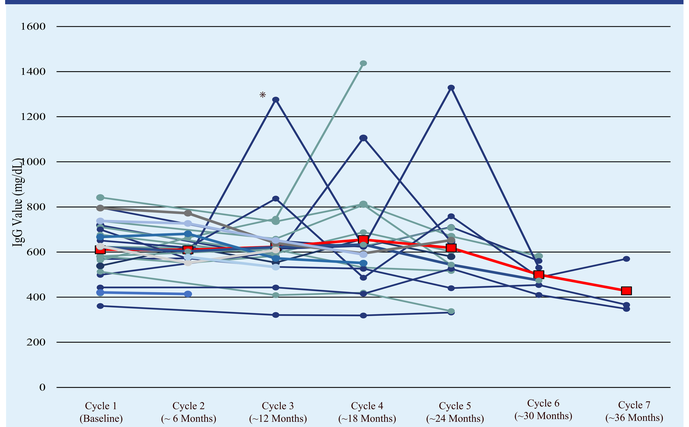
This study includes 354 patients receiving commercial OCR at The Elliot Lewis Center; 337 patients had baseline IgG levels available for analysis. Normal IgG values were defined as 600-1640 mg/dL. Subjects were monitored for infections and serious adverse events (SAEs). Subjects had biannual assessments of serum IgG levels and JCV antibody titers.

Results

Table 1: Patients with Decline in JCV Index ≥ 0.5

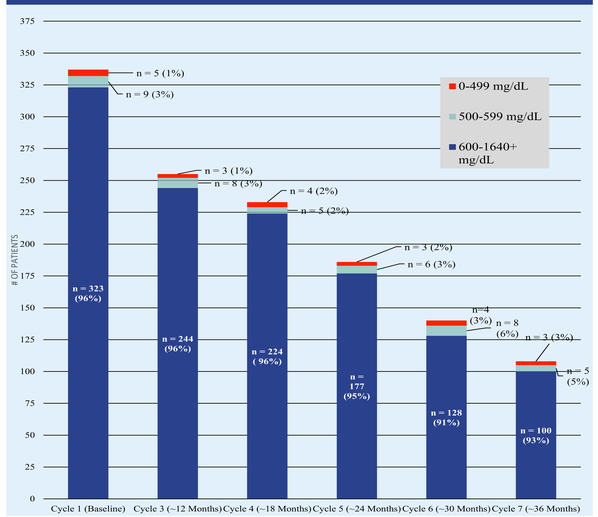
Subject #	Baseline JCV	Cycle 3 JCV	Cycle 5 JCV	Cycle 7 JCV	Baseline IgG	Recent IgG
1	1.55	---	1.03	---	1494	788
3	2.83	---	1.96	2.51	851	810
45	0.70	0.06	0.11	0.1	1100	1622
47	2.91	1.57	1.85	---	847	760
70	2.02	1.65	2.09	1.49	1368	872
89	1.40	0.28	0.27	0.35	624	500
101	2.11	0.92	0.71	---	738	542
118	1.82	1.35	1.01	1.18	981	654
120	2.62	1.56	1.37	1.58	634	659
135	3.48	2.82	---	---	1561	1391
158	2.81	1.69	1.48	1.34	569	366
200	3.29	1.83	0.99	---	970	1037
204	3.2	2.85	2.6	---	1056	916
236	3.80	3.21	3.21	3.35	1057	1112
249	3.81	3.18	2.67	---	1139	865
265	3.54	2.06	1.85	---	1328	1159

Figure 2: IgG Values in the Subset of Patients with Low IgG (<600mg/dL)



* Subject received IVIG

Figure 1: Number of Patients and IgG Values by OCR Cycle



- There was no downward trend in IgG levels in our patients, some of whom have received up to 7 cycles (36 months) of OCR.
- At baseline 323 patients had IgG >600mg/dL, and 14 had low IgG.
- 8 patients (2%) with low IgG (<600 mg/dL) at baseline remained low and 7 of those had at least one infection requiring antibiotics. One infection required hospitalization.
- 29 (9%) developed low IgG at some point, but only 8 patient remained low on follow up testing. 4 patients had single low values that returned to normal, and 3 patients developed single low IgG levels at their last treatment before the data cut.
- A higher rate of infection was not observed in patients with low IgG at baseline.

Discussion

In the OCR phase III clinical trials, low IgG levels occurred in a small percentage of patients, but the observation period was relatively short (4-5 treatment cycles),2,3 and patients with low baseline IgG were excluded. Experience with rituximab suggests that long-term B-cell depletion might lower IgG levels, leading to an increased infection risk. This is of particular concern in older patients with immunosenescence.

In the ACAPELLA cohort, no significant downward trend in IgG levels was observed in up to 36 months of treatment with OCR. Patients with low baseline IgG remained low but with no further decline. In our population, low IgG was not associated with a higher rate of infection.

A drop in JCV index levels has been reported with rituximab[4], but the impact of OCR on JCV antibody titers is not well described. 14 of 337 showed a drop in JCV index ≥ 0.5, and these JCV index changes were not associated with a decline in IgG levels.

Conclusion

- No significant downward trend in IgG levels was observed.
- Patients with low baseline IgG remained low but with no further decline.
- Low IgG was not associated with a higher rate of infection.

References
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