DXT67

ACAPELLA: Hypogammaglobulinemia and JCV Status in Ocrelizumab-Treated Patients

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Background

Ocrelizumab (OCR) is a humanized monoclonal anti-CD20 antibody approved for treatment of both relapsing remitting (RRMS) and primary progressive multiple sclerosis (PPMS). Hypogammaglobulinemia has been seen with other medications that induce long-term B-cell depletion and might be anticipated to occur with OCR[1]. During the phase III trials for OCR, immunoglobulin levels were monitored and patients with preexisting hypogammaglobulinemia were excluded. After 2-3 years of OCR treatment, a small proportion of patients developed low immunoglobulin G (IgG) values, but this was not associated with greater risk of infection[2]. The JCV IgG antibody index might also be affected by OCR, rendering the predictive value of JCV index invalid. 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 remains uncertain.

Objectives

As part of the ACAPELLA trial (a prospective study assessing OCR-associated adverse events in a real-world population, see poster DXT63), we evaluated the impact of OCR on immunoglobulin levels and JCV titers over time as well as any correlation between IgG levels and infection risk. In patients with low IgG, we evaluated immune function through measurement of specific antibody titers. This dataset reflects results collected through March 15, 2019.

Methods

This study includes all subjects receiving commercial OCR at The Elliot Lewis Center since its approval in March 2017. Subjects were monitored for occurrence of infections and other serious adverse events (SAEs) and had biannual assessments of serum immunoglobulin levels and JCV antibody titers. In patients with at least one low IgG value, antibody titers to tetanus, H. flu, and pneumococcus were measured.

Results

- 249 subjects have been enrolled in ACAPELLA; 235 (94%) had baseline IgG levels available.

Results (cont.)

- 23 subjects (10%) had low IgG (<694 mg/dL) at baseline.
- Of those 23 subjects, 15 have completed a minimum of one year of treatment. 12 of those 15 had persistently low IgG.
- 7 of 23 (30%) with low baseline IgG had at least one infection requiring antibiotics compared to 49/212 (23%) with normal IgG at baseline.°
- 212 subjects had normal (>694 mg/dL) IgG at baseline. 7 (3%) developed low IgG (6 after 2 cycles, 1 after 3 cycles), and all but one returned to normal.
- No SAEs occurred in any subject with low IgG.
- In subjects that received at least 4 cycles of OCR (18 months), no significant downward trend in IgG was observed.
- 99 subjects had JCV levels at baseline and cycle 3 (12 months), and 3 had a significant change in JCV status dropping from 1.4 to 0.28, 2.62 to 1.56, and 0.7 to 0.06 respectively.

° Not statistically significant (P = 0.4337)

Figure 1: IgG Values by OCR Cycle

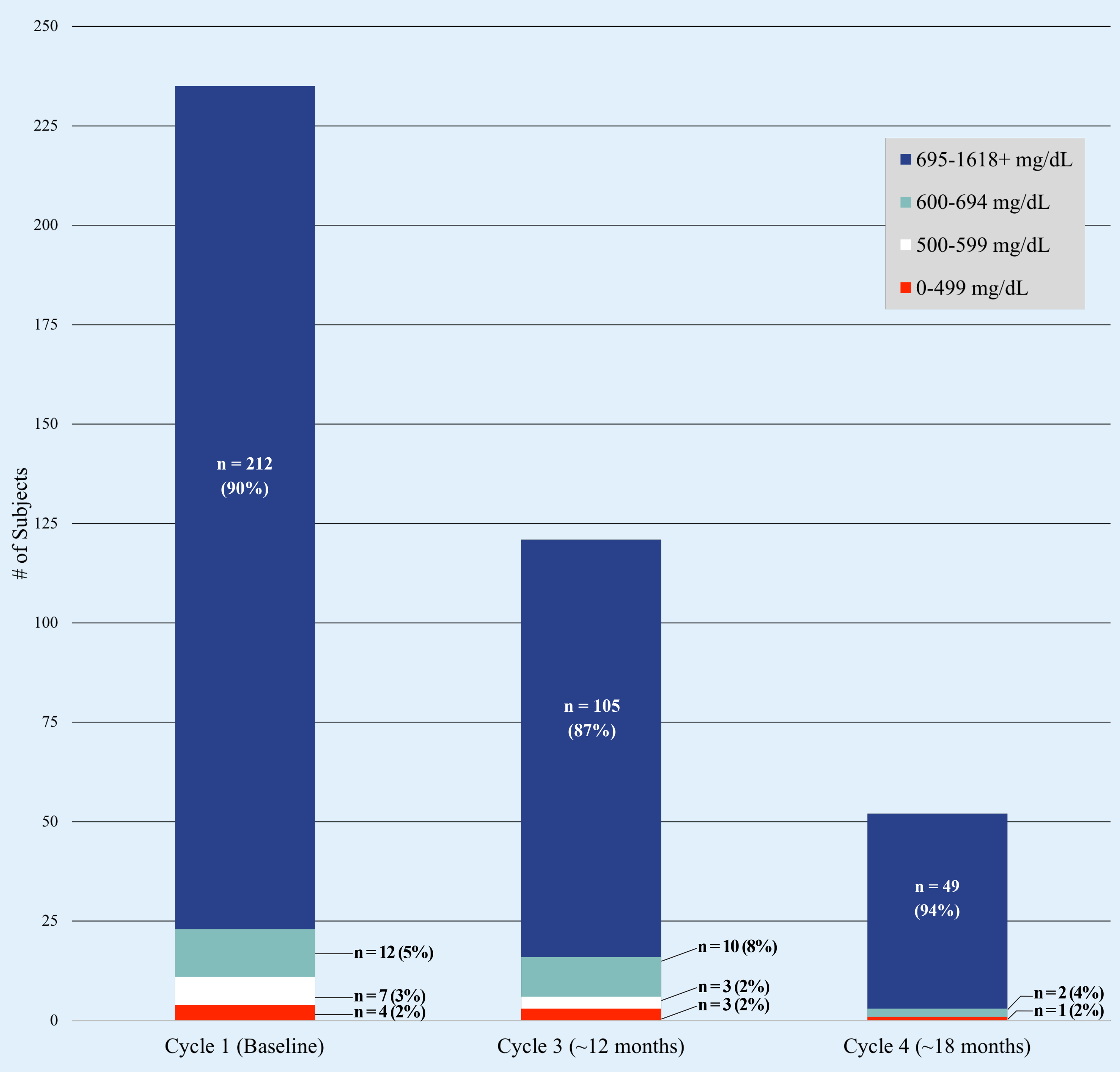
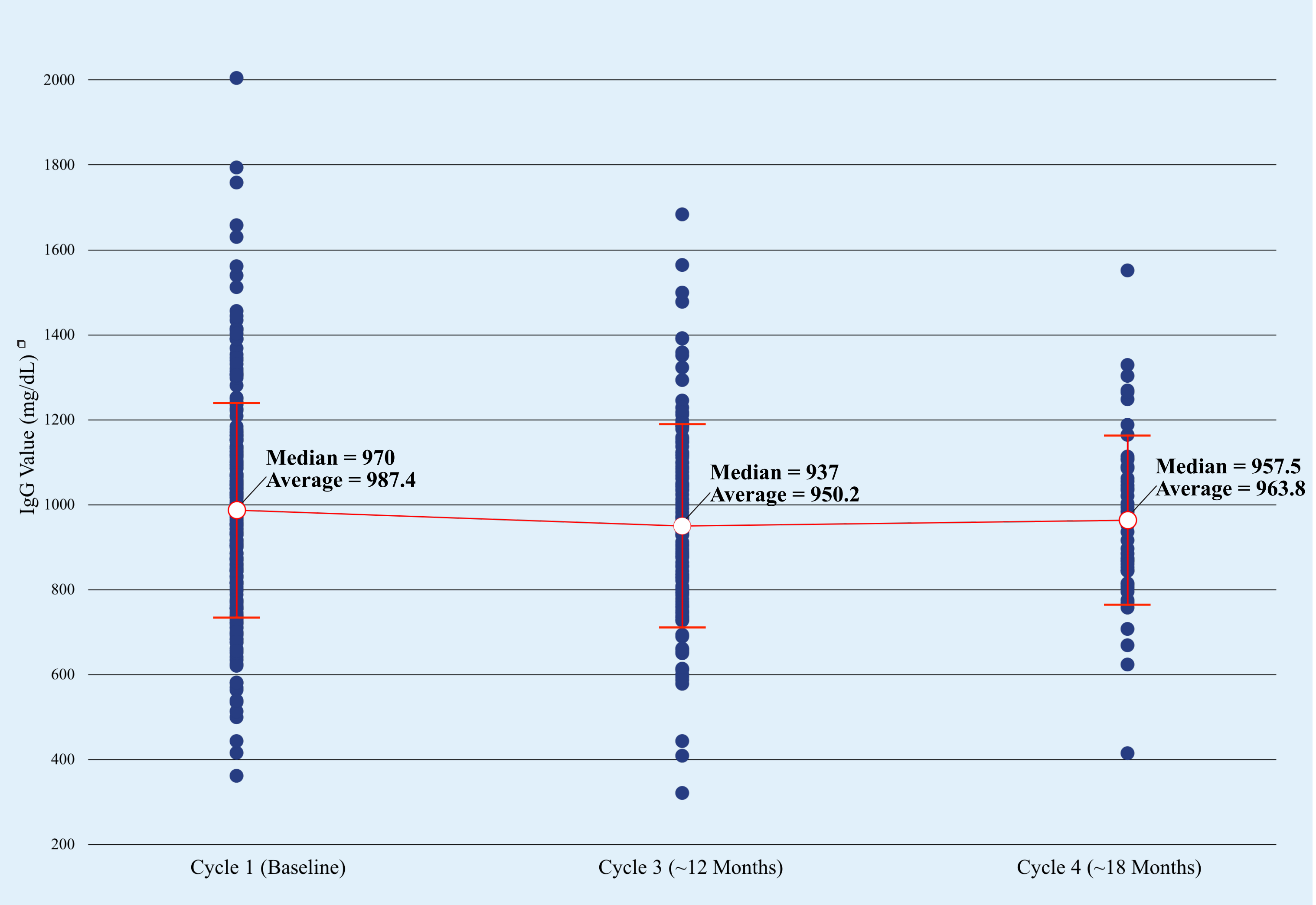
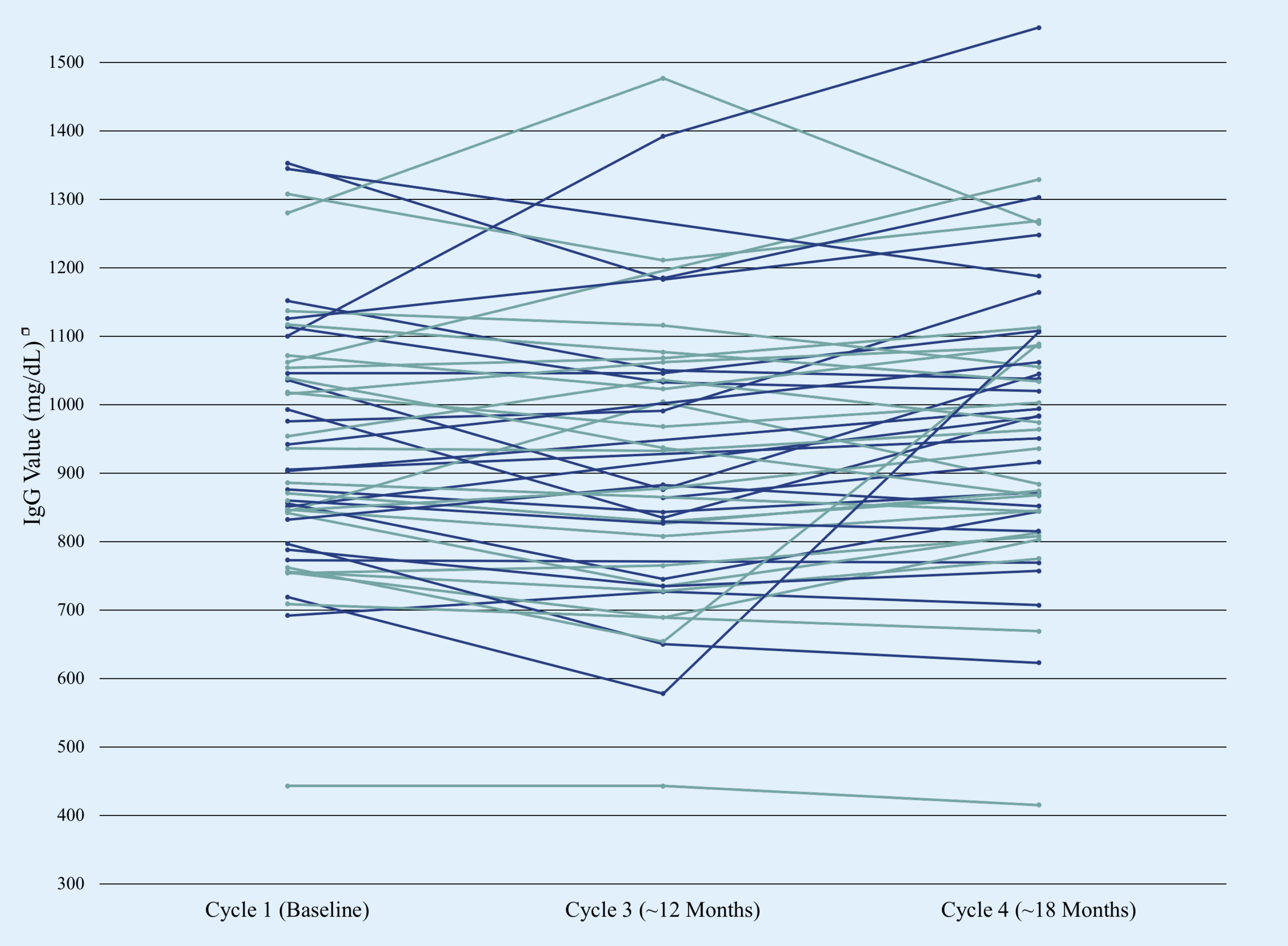


Figure 2: IgG Values by OCR Exposure



□ Values obtained on day of infusion

Figure 3: IgG Values in Subjects Dosed with 4 Cycles of OCR



□ Values obtained on day of infusion

Discussion

In the OCR phase III clinical trials, low IgG levels occurred in a small percentage of patients (1.5% in OPERA I & II and 1.1% in ORATORIO), but the observation period was relatively short (4-5 treatment cycles)[2,3]. Patients with low baseline IgG who might be at higher risk for infections were excluded from the clinical trials. Long-term B-cell depletion has the potential to lower IgG levels and increase the risk of infection. This is of particular relevance in older patients in whom immunosenescence further increases susceptibility to infection.

In the ACAPELLA cohort, no significant effect of OCR was seen on IgG levels after 12 or 18 months of treatment. We observed a trend suggesting that low baseline IgG levels may increase the risk of moderate infections, but no increase in serious infections was seen. In subjects with low IgG who did not develop protective immunity to H. flu and/or pneumococcus after vaccination, treatment with IVIG or antibiotic prophylaxis was considered depending on age and comorbidities.

A drop in JCV index levels has been reported with rituximab[4] and might be anticipated with long-term B-cell suppression, but the impact of OCR on JCV antibody titers is unknown. In one small study, JCV index was measured in ~25 patients receiving OCR and no significant impact on JCV levels was identified, but the duration of treatment was not reported. In the majority of our population, OCR treatment for 2-3 cycles (6-12 months) did not affect the JCV status. However, three patients had a significant change in JCV status after three cycles of treatment. Interestingly, these JCV index changes were not associated with a decline in IgG levels. The effect of long-term treatment has yet to be determined.

Conclusions

- 3-4 cycles (12-18 months) of OCR treatment did not have a significant impact on IgG levels
- Moderate infections were slightly more frequent in subjects with low baseline IgG
- The small number of patients with a substantial drop in JCV after three cycles suggests a possible future trend.

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, Egnore E et al. Anti-JC Virus Antibody Index Changes in Rituximab-Treated Multiple Sclerosis Patients. *Journal of Neurology,* 2018 Aug 14, 265: 2342
5. Stokmaier D, Winthrop K, Chognot C et al. Effect of Ocrelizumab on Vaccine Responses in Patients with MS. *Presented at the AAN Annual Meeting in Los Angeles, CA*, 2018 Apr 21-27; AAN Oral Presentation #S36.002.