Anti-EBV antibody reduction during ocrelizumab treatment is not associated with multiple sclerosis outcomes

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Introduction

The pathogenesis of multiple sclerosis (MS) involves genetic, environmental and immunological aspects. Epstein-Barr virus (EBV) infection is recognized as a major risk factor for MS, potentially contributing through infection and transformation of CD20 B cells. Monoclonal antibodies targeting CD20, such as ocrelizumab, may exert therapeutic effects by depleting memory B cells harbouring latent EBV. We aim to evaluate changes in serum anti-EBV immunoglobulin G (IgG) titres and clinical correlates during ocrelizumab treatment.

Methods

We analysed serum samples from 58 patients treated with ocrelizumab, with levels of total IgG, anti-CMV IgG, and anti-EBV IgG before treatment initiation and after mean follow-up of 4.8±1.5 years. Statistical analyses included paired t-tests to evaluate longitudinal changes in antibody levels, and linear regression models to investigate associations between IgG changes and relapse occurrence, MRI activity, EDSS progression and their combination.

Results

Over 4.8±1.5 years, we observed significant reductions in anti-EBV IgG (percentage mean change -8.2%, p=0.03), comparable to the decline in total IgG (-8.8%, p<0.01) and anti-CMV IgG (-7.8%, p<0.01). No significant associations were identified between changes in anti-EBV IgG and different outcomes.

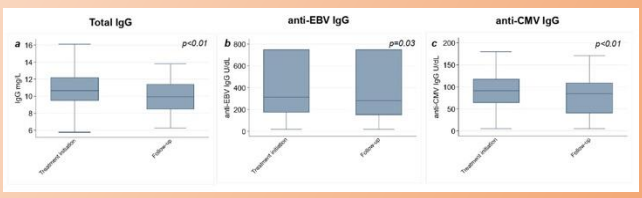

Figure 1. Changes in IgG levels.
Box-and-Whisker plots show levels of total IgG (a), anti-EBV IgG (b) and anti-CMV IgG (c) between baseline (treatment initiation) and follow-up (after 4.8±1.5 years). P-values are shown from paired t-test.

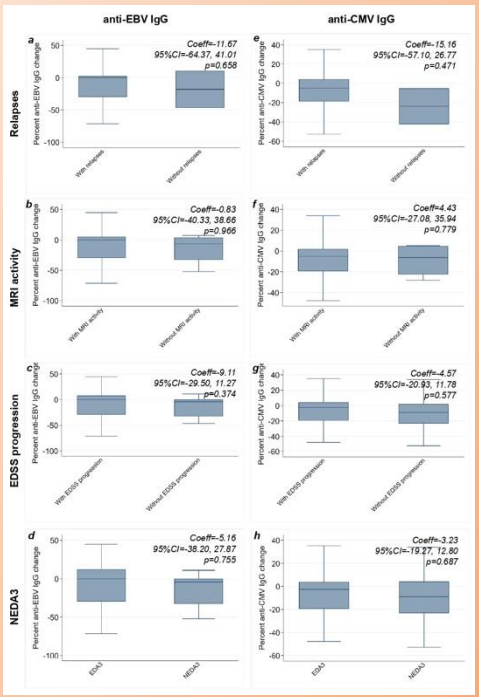

Figure 2. Clinical associations of IgG changes.
Box-and-Whisker plots show associations between percent changes in anti-EBV IgG and occurrence of relapses (a), MRI activity (b), EDSS progression (c) and NEDA3 (d), and between percent changes in anti-CMV IgG and occurrence of relapses (e), MRI activity (f), EDSS progression (g) and NEDA3 (h). Coefficients (Coeff), 95% confidence intervals (95%CI) and p-values are shown from linear regression models including percent changes of anti-EBV and anti-CMV IgG, in turn, as dependent variable, and occurrence of relapse, MRI activity, EDSS progression and NEDA3, in turn, as independent variable; covariates were age, sex, EDSS at treatment initiation, disease duration, treatment naive status, and follow-up duration.

Discussion

After nearly five years of ocrelizumab treatment, we observed a significant reduction in total IgG (-8.8%), anti-EBV IgG (-8.2%), and anti-CMV IgG (-7.8%). The similar decline across all antibody types suggests that ocrelizumab induces a **general suppression of humoral immunity** rather than a selective decrease in EBV-specific antibodies. Importantly, no associations were found between changes in total, anti-EBV, or anti-CMV IgG levels and **clinical or radiological MS outcomes** (relapses, MRI activity, EDSS progression, or NEDA3 status).

Our findings align with previous studies showing reduced anti-EBV IgG levels following B-cell depletion, confirming the expected pharmacodynamic effect of ocrelizumab. However, these changes do not appear to influence disease activity or progression. It remains possible that **EBV-specific T-cell responses**, also modulated by ocrelizumab, play a more relevant role in MS immunopathology, possibly through **molecular mimicry** mechanisms linking EBV antigens to myelin proteins.

The main limitations of this study include the **small sample size**, the **absence of early longitudinal sampling**, and the **restriction to anti-VCA IgG measurement** without evaluation of other EBV-specific markers (e.g., anti-EBNA1). Therefore, while ocrelizumab induces broad immunoglobulin reduction, our data cannot exclude a potential pathogenic contribution of EBV in MS.

Conclusion

Our study shows no correlation between anti-EBV IgG levels and MS worsening during ocrelizumab therapy. While ocrelizumab significantly reduces total IgG levels, including anti-EBV IgG and anti-CMV IgG, this effect appears to reflect a general dampening of humoral immunity rather than a targeted modulation of EBV-infected B cells. These findings suggest that the clinical efficacy of ocrelizumab is unlikely to be directly mediated through changes in EBV-specific humoral responses. Further research in larger cohorts is warranted to better elucidate the complex immunological interplay between EBV, B-cell–depleting therapies, and MS worsening.

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