

The Effect of Ocrelizumab on JC Virus Antibody Index

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Introduction:

The JCV antibody index is a two-step ELISA to detect antibody to VP1, a JCV structural protein. This test that has been validated as a risk factor for progressive multifocal leukoencephalopathy (PML) with natalizumab and often employed with other disease modifying therapies that carry a risk of PML though not validated in the latter population. Higher titers of the JCV antibody index have correlated with an increased risk of natalizumab associated PML.(Plavina, Subramanyam et al. 2014)

In the phase 3 trials of ocrelizumab, an anti-CD20 monoclonal antibody, for primary progressive multiple sclerosis, levels of IgG and IgA in treated and placebo groups generally remained above the lower limit of normal during the controlled treatment period; however, IgM levels were below the lower limit of normal in 15.5% of ocrelizumab treated patients compared to 1.2% of controls.(Montalban, Hauser et al. 2017) In subsequent studies, low levels of IgG have also been reported in small proportions of patients being treated with ocrelizumab (Tran et al 2019; Evertsson et al, 2020) and may result in lower IgG levels than treatment with rituximab (Evertsson et al 2020).

In light of the potential of ocrelizumab to reduce immunoglobulin levels, this study is designed to determine whether the administration of ocrelizumab has an effect on the JCV antibody index, a test that has been validated as a risk factor for progressive multifocal leukoencephalopathy (PML) with natalizumab and often employed with other disease modifying therapies that carry a risk of PML though not validated in the latter population

Background on the JCV antibody index:

The seminal study of JCV antibody serostatus with the JCV antibody index demonstrated that the overall prevalence was 56.0% in the in a study of 1,096 MS patients with a false-negative rate of 2.7%.(Bozic, Richman et al. 2011) This initial study showed that seroprevalence was lower in females and increased with age.(Bozic, Richman et al. 2011) An increase in JCV seropositivity with age has been observed with other assays(Antonsson, Green et al. 2010) as well including the earliest studies that employed a hemagglutination assay. A variety of studies have demonstrated seropositivity rates varying between 55%(Aladro, Terrero et al. 2016) and 72%(Hegen, Auer et al. 2017) for the JCV antibody index in the population. Geographic differences in JCV serostatus are noted with the JCV antibody index with JCV seropositive status ranging from approximately 47% to 68% depending on country.(Olsson, Achiron et al. 2013) In longitudinal studies, fluctuation in the antibody status from seronegative to seropositive or the converse has been reported from as low as 4%(Plavina, Subramanyam et al. 2014) to 17%(Aladro, Terrero et al. 2016) with intermediate values reported by other investigators(Aladro, Terrero et al. 2016, Alroughani, Akhtar et al. 2018) Unsurprisingly, seronegative individuals with the lowest titers antibody titers tend to remain seronegative over time and those who are seropositive with high titer JCV antibody indices tend to remain seropositive.(Hegen, Auer et al. 2017) One study suggested that anti-JCV antibody index levels >0.90 predicted stable seropositive status,(Kolcava, Hulova et al. 2019) though that finding has not been universally observed. Most studies have demonstrated an increase in the seroprevalence to JCV antibody with age which may be attributable to either recent exposure to the virus or, alternatively, an anamnestic response in which JCV replication in an individual who has been latently or persistently infected with the virus results in levels of antibody that reach the threshold for seropositivity. Few studies have explored whether disease modifying therapy for MS with immunosuppressive therapies has an effect on the JCV serostatus. One study suggested that immunosuppression including natalizumab exposure had no effect on serostatus over time;(Bozic, Richman et al. 2011, Aladro, Terrero et al. 2016) however, other studies have disputed that observation. For instance, a Swedish study found that natalizumab initiation was associated with a decrease in anti-JCV antibody levels(Warnke, Ramanujam et al. 2013) and Peters and Williamson at the University of Pennsylvania found that individuals on natalizumab more frequently converted from seronegative to seropositive than those exposed to other DMTs (23.9% v 9.1%, p<0.01) and trended to higher levels of JCV antibody index levels over time.

Objectives:

The objective of this study to determine whether long-term administration of ocrelizumab has an effect on JCV antibody levels as determined by the widely used JCV antibody index. The hypothesis to be tested is that ocrelizumab's effect on plasma cell populations will reduce JCV antibody index levels over time as has been suggested with at least two small studies of the effect of rituximab on anti-JCV antibody index.(Friedman-Urevich, Gottesman et al. 2017, Baber, Bouley et al. 2018)

1 Primary outcome measure:

- The primary outcome measure will be the magnitude of decline in the anti-JCV antibody index over the course of 2 years of ocrelizumab treatment.

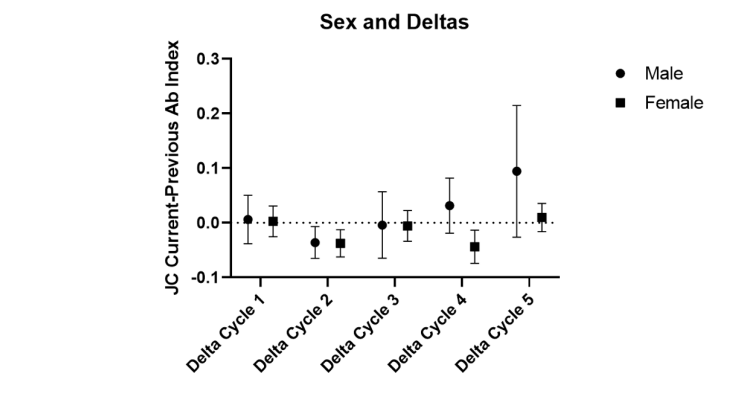
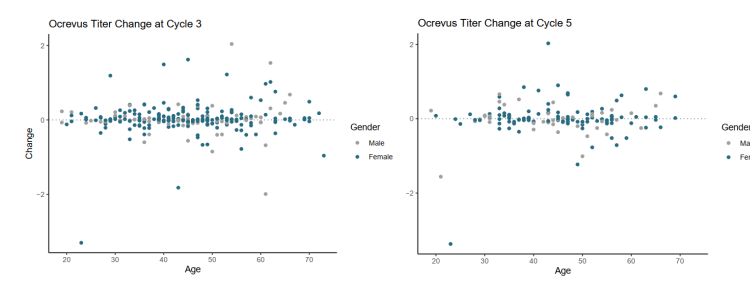
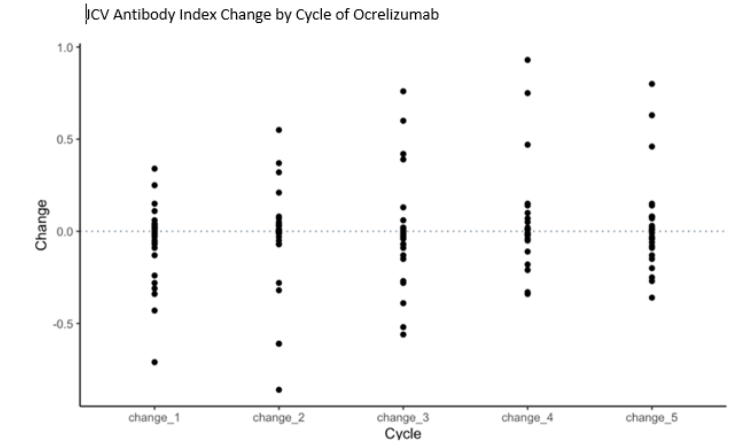
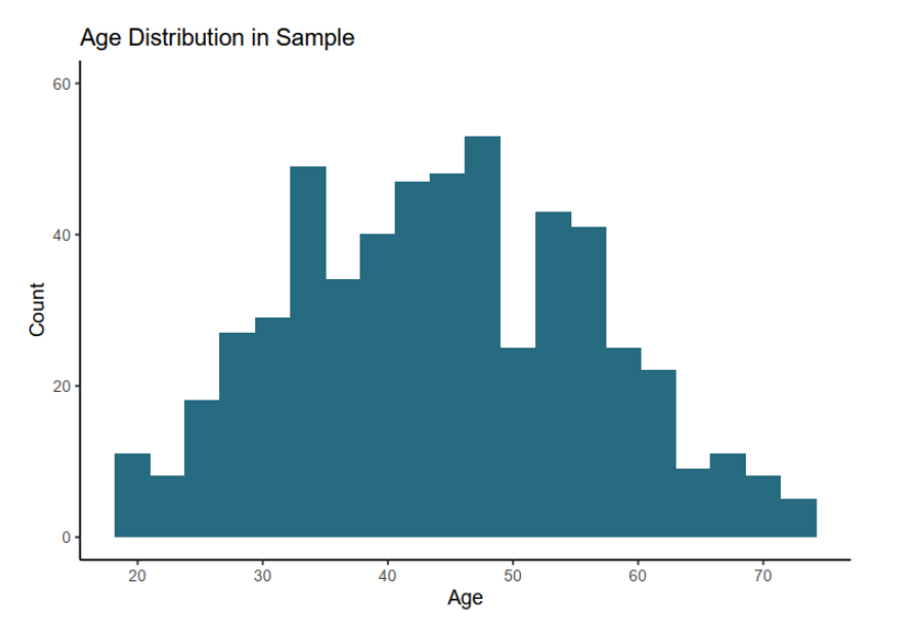
2 Secondary outcome measures:

- A secondary outcome measure will be the rate of conversion from JCV antibody seropositive at study entry to indeterminate or seronegative over the 2-year course of the study.

Study Design:

This was a longitudinal study of the effects of ocrelizumab on JCV antibody index levels. JCV antibody index will be obtained in all patients on ocrelizumab and repeated at semiannual intervals over the course of 2 years or longer. JCV antibody index was assessed proximate to the time of ocrelizumab initiation and compared with those obtained in the ensuing 2 years.

JCV antibody index were recorded at approximately 6-month intervals over a 2-year period in 645 persons with multiple sclerosis. JCV antibody index levels were available before the initiation of treatment in 560. The initial JCV antibody index level was compared to that after 2-years of treatment. Variables such gender, age at treatment initiation, prior DMT, immunoglobulin levels were also recorded.



Results:

Of the 560 patients in whom JCV antibody index using STRATIFY JCV ELISA (Quest Diagnostic, San Juan Capistrano, CA) was assessed prior to the initiation of ocrelizumab, 360 (54.6%) were JCV seropositive (>0.4) and 200 (45.4%) were seronegative (0.0-0.20) or indeterminate (0.2-0.4).

Over the course of 2 years, among those individuals who were JCV seropositive, there was a small though statistically significant trend towards lower antibody titers; however, no individuals became persistently seronegative.

The average decline in the JCV antibody index was 0.257 (95% CI-0.318 to -0.196). In a small number of individuals, there was a reclassification at repeat testing between seronegative, indeterminate, and seropositive, but only 3 individuals who were seronegative at initial assessment converted to seropositive status at 2 years.

Conclusions:

This study confirms the following

- A small though statistically significant trend to lower JCV antibody index titers in individuals treated with ocrelizumab over 2 years.
- The small number of individuals becoming seropositive during the course of treatment is in keeping with the observation in other populations and is unlikely to have been the effect of the therapy.
- Age and gender had no effect on antibody index levels. Additional factors, e.g., immunoglobulin levels, absolute B cell counts and percentages, will be correlated with the JCV antibody response in future analyses.
- The rarity of PML with ocrelizumab and the results from this study indicate that measuring JCV antibody index in this population is unlikely to be of any prognostic value.

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