

## Editorial

# Pinning our Hopes on Anti-CD20 Therapy

**Sloane JA\***

Department of Neurology, Beth Israel Deaconess Medical Center, USA

**\*Corresponding author:** Jacob A. Sloane, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, USA**Received:** May 17, 2016; **Accepted:** May 18, 2016;**Published:** May 20, 2016**Editorial**

Anti CD20 treatments represent a novel approach to the treatment of Multiple Sclerosis (MS). Before clinical trials showed efficacy of anti-CD20 treatments in MS, MS was considered primarily a T cell-mediated disease, clearly naive in retrospect. With the development of anti-CD20 treatments, the MS community realized B cells also contribute to MS pathogenesis probably through antigen presentation [1], but this has yet to be clearly established.

The first study on anti-CD20 treatment (HERMES) showed beneficial effects of rituximab in Relapsing Remitting MS (RRMS) in terms of improved clinic radiological outcomes [2]. In addition, some positive effects for anti-CD20 treatment were shown in a small study of rituximab in Primary Progressive MS (PPMS) (OLYMPUS) but the study overall did not show significant benefit in PPMS [3].

Although rituximab has been used to treat rheumatoid arthritis and B cell lymphoma since 2006, another anti-CD20 treatment, ocrelizumab, was more recently created and tested in MS clinical trials (OPERA I/II for RRMS and ORATORIO for PPMS) [4,5]. Very likely financial considerations drove the creation of ocrelizumab. However, one potential benefit of ocrelizumab could have been greater humanization of ocrelizumab reduced infusion reactions associated with rituximab. Unfortunately, that did not turn out to be true in clinical trials. Nevertheless, new data on ocrelizumab indicates very good efficacy in RRMS (OPERA I/II) [5]. Ocrelizumab showed a significant 47% reduction in adjusted annualized relapse rate compared to IFN $\beta$ 1a. Ocrelizumab also reduced clinical progression by 40% at 6 months and brain atrophy by 19% compared to IFN $\beta$ 1a.

In addition, ocrelizumab has been shown to slow progression in PPMS (ORATORIO) [4]. At first blush, this effect could be driven by similar mechanisms as in the RRMS trials. Gadolinium enhancing lesions were observed in a high percentage of patients involved in this study. Ocrelizumab could have exerted benefit by limiting appearance of enhancing lesions in PPMS. However, further analysis has shown no significant difference in outcomes between patients with and without enhancing MRI lesions, suggesting effects on progression arose from other effects of ocrelizumab independent of effects on enhancing lesions.

Considering the OLYMPUS trial in a similar light potentially makes interpretation of ORATORIO results more difficult. In OLYMPUS, rituximab did not appear to have a benefit for PPMS patients overall [3]. Subgroup analysis indicated young patients and

patients with enhancing lesions significantly benefited in terms of progression. As with rituximab, PPMS patients with no enhancing lesions still may have limited benefit from ocrelizumab. Time will tell whether ocrelizumab works only by limiting active demyelination or by other means.

In spite of these controversies, ocrelizumab is primed to take over a sizeable portion of the MS treatment market. Most clinicians are impressed with the strong efficacy in RRMS and will likely employ ocrelizumab in treating aggressive RRMS. Ocrelizumab will be extensively used in PPMS as well as SPMS since progression may be slowed similarly. Ocrelizumab will also be useful for JCV antibody positive patients on natalizumab. PML risk on natalizumab increases with JCV antibody positivity, and increasingly so with higher titers [6]. Overall risk on natalizumab averages 1:1000, but can be as high as 1:90. In contrast, there have been no cases of PML for patients on ocrelizumab, although early. Rituximab has an estimated risk of PML of approximately 1:25,000 [7]. Since rituximab is extensively utilized in rheumatology and oncology where rituxan is used with chemotherapy, PML risk from anti-CD20 treatment will most likely be even lower in MS patients without exposure to chemotherapy. Therefore, risk of PML should be drastically reduced in JCV antibody positive patients who switch from natalizumab to ocrelizumab. Overall, ocrelizumab appears to be an exciting and widely useful addition to the slew of MS treatments already available.

Several questions remain for ocrelizumab, and some very concerning. The most important concern is PML in the ocrelizumab-treated patient. Whereas approximately 75% patients survive natalizumab-related PML, survival on rituximab appears quite limited at about ~10% with lymphoma and autoimmune disease [8]. Unfortunately, PML will occur with ocrelizumab use in the MS population, especially those switching from natalizumab. Based on the literature of PML and anti CD20 treatment, PML on ocrelizumab will very likely be lethal. This contrasts starkly to all other MS treatments with PML risk (natalizumab, dimethyl fumarate, and fingolimod).

Since many clinicians will switch the JCV antibody positive natalizumab treated patient to ocrelizumab, this type patient may be particularly concerning in PML risk. If asymptomatic PML forms in the natalizumab treated patient before switch, PML could progress and potentially cause death on ocrelizumab. To be cautious, a good approach may be to perform MRI just prior to ocrelizumab start to rule out any PML. It may make sense to have a large gap in treatment to flush out natalizumab prior to ocrelizumab start. However, a gap in treatment longer than 4-8 weeks could increase risk of relapse and natalizumab-related rebound [9]. Finally, a very small subset of patients without PML have JC virus in their CSF [10] and ocrelizumab may best be avoided in these patients. It is unknown whether clinicians should assess patients for the presence of JC virus in CSF prior to ocrelizumab.

Long term safety of ocrelizumab is another concern. Data indicate ~50% of patients treated with rituximab acquire

hypogammaglobulinemia in the long term [11]. Hypogammaglobulinemia increases risk of infection and can be prevented by IVIG treatments, which add back immunoglobulin to normalize levels [12]. Therefore, this risk from hypogammaglobulin is surmountable. How common hypogammaglobulinemia occurs with long term ocrelizumab treatment remains to be determined.

Lastly, other anti-CD20 treatments may cut into the large ocrelizumab market in the near future. Initial work with ofatumumab, another anti-CD20 treatment, shows very promising effects in MRI related changes in RRMS [13]. Ofatumumab trials are ongoing, and are studying an injectable formulation that can be given at home. Since progressive MS patients have limited mobility, ofatumumab may be easier to use for these patients. Much remains to be done with ofatumumab, however, before it can compete with ocrelizumab. Overall, ocrelizumab will substantially augment the armamentarium of treatments to fight MS and its future looks very bright.

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