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Editorial

Pinning our Hopes on Anti-CD20 Therapy

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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 IFNß1a. Ocrelizumab also reduced clinical progression by 40% at 6 months and brain atrophy by 19% compared to IFNß1a.

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.

Inspite 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

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hypogammaglobinemia in the long term [11]. Hypogammaglobinemia 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 hypogammaglobinemia 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 ofatumamab, another anti-CD20 treatment, shows very promising effects in MRI related changes in RRMS [13]. Ofatumamab trials are ongoing, and are studying an injectable formulation that can be given at home. Since progressive MS patients have limited mobility, ofatumamab may be easier to use for these patients. Much remains to be done with ofatumamab, 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.

References

1. Claes N, Fraussen J, Stinissen P, Hupperts R, Somers V. B Cells Are Multifunctional Players in Multiple Sclerosis Pathogenesis: Insights from Therapeutic Interventions. Front Immunol. 2015; 6: 642.
2. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008; 358: 676-688.
3. Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, et al. OLYMPUS trial group. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol. 2009; 66: 460-471.
4. Montalban X, Hemmer B, Rammohan Kottil, Giovannoni G, De Seze J, Bar-Or A, et al. Efficacy and safety of ocrelizumab in primary progressive multiple sclerosis: results of the phae III double-blind, placebo-controlled ORATORIO study. Ann Neurol Conference. 2016.
5. Hauser SL, Arnold DL, Bar-Or A, Comi G, Hartung H, Lublin F, et al. Efficacy of Ocrelizumab in Patients with Relapsing Multiple Sclerosis: Pooled Analysis of Two Identical Phase III, Double-Blind, Double-Dummy, Interferon Beta-1a-Controlled Studies. Ann Neurol Conference. 2016.
6. Plavina T, Subramanyam M, Bloomgren G, Richman S, Pace A, Lee S. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol. 2014; 76: 802-812.
7. Clifford DB, Ances B, Costello C, Rosen-Schmidt S, Andersson M, Parks D, et al. Rituximab-associated progressive multifocal leukoencephalopathy in rheumatoid arthritis. Arch Neurol. 2011; 68: 1156-1164.
8. Carson KR, Evens AM, Richey EA, Habermann TM, Focosi D, Seymour JF, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood. 2009; 113: 4834-4840.
9. Fox RJ, Cree BA, De Sèze J, Gold R, Hartung HP, Jeffery D, et al. MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study. Neurology. 2014; 82: 1491-1498.
10. Chalkias S, Dang X, Bord E, Stein MC, Kinkel RP, Sloane JA, et al. JC virus reactivation during prolonged natalizumab monotherapy for multiple sclerosis. Ann Neurol. 2014; 75: 925-934.
11. Roberts DM, Jones RB, Smith RM, Alberici F, Kumaratne DS, Burns S, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmune. 2015; 57: 60-65.
12. Md Yusof MY, Vital EM, Buch MH. B cell Therapies, Approved and Emerging: a Review of Infectious Risk and Prevention During Use. Curr Rheumatol Rep. 2015; 17: 65.
13. Sorensen PS, Lisby S, Grove R, Derosier F, Shackelford S, Havrdova E. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. Neurology. 2014; 82: 573-581.

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