Should ocrelizumab be used in non-active primary progressive multiple sclerosis? Time for a re-assessment

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Anti-CD20 therapies have been approved for patients with multiple sclerosis (MS). Based on their efficacy, they have informed on the pathogenic role of CD20-positive B-cell and T-cell subsets in central nervous system (CNS) autoimmunity.

Ocrelizumab, a humanized recombinant monoclonal anti-CD20 antibody was also the first agent to be approved for patients with primary progressive multiple sclerosis (PPMS) based on the results of the phase III randomized placebo controlled multicenter trial ORATORIO.[1] In particular, ocrelizumab was found to have a significant benefit over placebo in reducing confirmed disability progression at 12 weeks. However, ocrelizumab was not the first anti-CD20 therapy that was tried in patients with PPMS. Rituximab, a chimeric recombinant monoclonal antibody had previously been tested against placebo in patients with PPMS in the phase II/III OLYMPUS trial, and the primary disability-based outcome identical to the one utilized in the ORATORIO trial was not met.[2] Other than their immunogenicity, ocrelizumab and rituximab are presumably very similar agents, and there is no evidence that their mechanism of action or potency would be fundamentally different.[3] Then what could be the explanation for the differences in outcomes between the ORATORIO and OLYMPUS trials?

The main discernable difference between the trials may be the age of the study participants. OLYMPUS enrolled patients between the ages of 18 and 65 years, with an average age of 49.9 years.[2] Indeed, age was a major factor in driving a rituximab treatment effect: a pre-planned analysis demonstrated that confirmed disability progression was delayed in patients younger than 51 years of age.[2] ORATORIO, presumably based on the observations made in the OLYMPUS trial, enrolled patients between 18 and 55 years of age.

The change of inclusion criteria likely led to the enrichment of the trial with patients who still had some form of active disease as defined by Lublin *et al.*, namely disease activity on brain magnetic resonance imaging (MRI).[4] Our current understanding of active disease focuses on inflammation-related relapses, or MRI signal changes. It is, however, conceivable that there might be active degeneration without immunological activity, a potential event that is currently incompletely understood clinically, radiologically, and histologically.

Consequent to the afore-mentioned changes in the inclusion criteria, patients enrolled in ORATORIO were on average between 44 and 45 years old.[1] While subsequent sub-analyses could not detect a significant difference regarding the response to ocrelizumab in ORATORIO between active primary progressive multiple sclerosis (APPMS) and non-active primary progressive multiple sclerosis (NAPPMS) patients, the trial was not powered to show such a difference.

Going forward, recipients of ocrelizumab will be designated O-APPMS or O-NAPPMS, whereas individuals in the placebo group will be designated P-APPMS or P-NAPPMS. Disease activity, namely clinical relapses and new or inflammatory signal changes on MRI are thought to be driven by the influx of adaptive and innate immune cells from the periphery into the CNS with or without neurodegenerative disease, whereas NAPPMS is considered the neurodegenerative disease stage that is largely independent of peripheral immune cells.[5] In active MS, most approved agents reduce the absolute number of immune-competent cells, or sequester them out of the brain or spinal cord.

Neurofilament light chain (NfL) is a scaffolding protein that is abundantly expressed in the axons and dendrites of neurons in the CNS and peripheral nervous system (PNS).[6] Serum NfL levels have been shown to track well with MS disease activity and treatment responses at a group level, and can be reliably and reproducibly detected at single-digit picogram levels with a SIMOA assay. It is currently thought that 3-monthly NfL assessments provide an uninterrupted reflection of axonal and dendritic loss during the observation period. There is good plausibility to believe that serum NfL is a meaningful marker of neurodegeneration in MS. However, NfL is also elevated in the setting of neuroinflammation that results in neurodegeneration.

For the purpose of an argument that NfL is a feasible biomarker to test the effects of ocrelizumab on neuroinflammation or neurodegeneration, one needs to assume that there is no CD20-expressing cell-mediated neuroinflammation in the absence of clinical or imaging disease activity. Based on the clinical and imaging outcomes of ORATORIO, the following possible outcome interpretations regarding a reduction in serum NfL levels, or in preventing their increase during the study period, are biologically plausible:

1. Patients in the O-APPMS group benefit significantly more than O-NAPPMS, P-AAPMS, and P-NAPPMS patients. This outcome would indicate a primary anti-inflammatory effect of ocrelizumab in patients with PPMS.
2. Patients in the O-NAPPMS group benefit significantly more than O-APPMS, P-AAPMS, and P-NAPPMS patients. This outcome would indicate a primary neuroprotective effect of ocrelizumab in patients with PPMS.
3. Patients in the O-APPMS and O-NAPPMS groups benefit significantly more than P-APPMS and P-NAPPMS patients. This outcome would support the use of ocrelizumab in all patients with PPMS and may suggest anti-inflammatory and neuroprotective effects of ocrelizumab.
4. Patients in the O-APPMS and O-NAPPMS groups benefit significantly more than P-APPMS but no more than the P-NAPPMS group. This outcome would indicate a primary anti-inflammatory effect of ocrelizumab in patients with APPMS.

Other investigators recently presented data on 12-weekly blood NfL assessments during ORATORIO.[7] The results are not currently available in published form. Essentially, ocrelizumab had no effect on blood NfL levels in patients with PPMS who did not have gadolinium-enhancing lesions prior to enrollment, namely patients with NAPPMS. According to the afore-mentioned possible interpretations, there is no evidence that ocrelizumab has neuroprotective effects. The beneficial effects of ocrelizumab in PPMS are driven mostly or entirely by its anti-inflammatory properties. Evidently, ocrelizumab benefits the same MS patient populations as other currently approved disease-modifying therapy (DMT), namely patients with inflammatory active MS.

This manuscript is an expert consensus statement meant to address gaps in clinical decision-making regarding the biological effects of ocrelizumab in patients with PPMS. These gaps exist because there are insufficient data to inform treatment guidelines. The level of evidence of our assessment is level 5 based on criteria established by the Centre for Evidence-Based Medicine, Oxford (https://www.cebm.net/).

The afore-mentioned analyses are meaningful and should be impactful for guiding the therapeutic decisions in patients with PPMS who are being treated with ocrelizumab, or who are being considered for treatment with ocrelizumab. Patient selection is always critical for any intervention. For anti-CD20 agents it was recently demonstrated that prolonged therapy significantly increases the risk of serious infections.[8] This observation indicates that there should be a constant evaluation of all biochemical and biological data to ascertain the best risk:benefit ratio for all patient subgroups.[9] Findings from biomarker studies should not be ignored by regulators or treating physicians. This is especially true in markets where ocrelizumab is approved for all patients with PPMS.

Conflict of interest

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