MULTIPLE SCLEROSIS

Beyond ocrelizumab in primary progressive multiple sclerosis?

Thomas Williams and Jeremy Chataway

Currently, the anti-CD20 monoclonal antibody ocrelizumab is the only approved treatment for primary progressive multiple sclerosis (PPMS). However, a new study suggests that other immunomodulatory disease-modifying therapies often used to treat relapsing forms of multiple sclerosis could be effective in people with PPMS who have evidence of active inflammatory disease.

Refers to Portaccio, E. et al. Disease-modifying treatments and time to loss of ambulatory function in patients with primary progressive multiple sclerosis. *JAMA Neurol.* https://doi.org/10.1001/jamaneurol.2022.1929 (2022).

In medicine, randomized controlled trials (RCTs) provide the bedrock for determining whether a clinical intervention is likely to be effective. Randomisation results in groups of participants that are balanced (not withstanding chance) with respect to both known and unknown confounders[1]. RCTs in multiple sclerosis (MS) have been a particular success story, resulting in the approval of over 15 compounds to treat the relapsing form of the disease[2]. To date, however, the anti-CD20 monoclonal antibody ocrelizumab is the only agent to be approved by the FDA and the European Medicines Agency (EMA) for the treatment of PPMS, following the publication of the ORATORIO trial in 2017[3].

ORATORIO demonstrated a 24% relative risk reduction in 12-week confirmed disability progression on the Expanded Disability Status Scale (EDSS) compared with placebo. The effect

was positive across the whole trial cohort, but pre-specified secondary analyses demonstrated a greater effect in younger patients and those with evidence of active inflammatory disease. Indeed, in the context of progressive MS, the EMA restricts ocrelizumab use to people with early PPMS, who also have imaging features of inflammatory activity[4]. In a new study published in *JAMA Neurology*[5], Portaccio et al. ask whether any immunomodulatory disease-modifying treatments (DMTs) could produce a treatment effect in the subgroup of individuals with PPMS who have ongoing inflammatory activity.

Once initial RCT evidence has been gathered, data from large registries, combined with techniques such as propensity matching, can be used to ask questions regarding the durability of the effect over a longer time period; the applicability of the results to a more diverse population (for example, with regard to age or ethnicity); the potential interactions with comorbidity; and the relative effectiveness and optimal timing of different DMTs. Examples of propensity-matched observational analyses in the MS field have come from the MSBase registry. This international collaboration includes over 80,000 patient records with up to 18 years of follow-up. Important analyses from this data set include the demonstration that in relapsing–remitting MS (RRMS), higher efficacy and earlier use of DMTs are associated with reduced risk of future disability milestones[6,7]. In people with secondary progressive MS (SPMS), ongoing relapses are a poor prognostic factor, with greater risk of reaching EDSS 7.0 (that is, unable to walk more than 5 m, even with aid, hence essentially wheelchair dependent). In people with SPMS who continue to experience relapses, however, greater use of DMTs is associated with a significantly reduced risk of progression[8].

Using a similar approach, Portaccio et al.[5] examined data from the Italian MS registry, including participants with PPMS according to the ORATORIO trial entry criteria (BOX 1). As in the MSBase analyses, the primary outcome was the risk of meeting the fixed and vital

milestone of EDSS 7.0. People with PPMS were matched on their propensity to be initiated on any DMT during the period of observation, as compared with those who remained untreated throughout. The researchers controlled for potential confounders including age at onset, age at baseline, sex, baseline EDSS score, frequency of patient visits and presence of relapses in the year before baseline. Cox regression models were then used to compare the treated and untreated groups with regard to the risk of permanently reaching EDSS 7.0 during follow-up.

From an initial total cohort of 3,298 individuals, 409 (12%) were included in the matched comparison. 288 (70%) initiated treatment during a mean follow-up duration of around 10 years, and were compared with 121 who remained untreated. Of note, none of the patients in the treated group were initiated on ocrelizumab, and only a minority were switched to ocrelizumab during follow-up. Therefore, most of the individuals in the treatment group were taking DMTs not licenced for PPMS, which were classified as moderately or highly effective on the basis of previously established efficacy data. Propensity matching enabled confounding between the comparison groups to be minimized, although on average the untreated individuals were slightly older and had longer disease durations and higher baseline EDSS compared with the treated group. The cohort displayed a relatively high degree of inflammatory disease activity, with around one-third experiencing a relapse during follow-up.

As in people with SPMS, superimposed relapses during follow-up were associated with a higher risk of developing EDSS 7.0[5]. Initiation of DMT was also associated with an increased risk of reaching EDSS 7.0, perhaps reflecting the tendency for such treatments to be started in patients deemed by their neurologist to have a poor prognosis. The key finding, however, was a significantly reduced adjusted hazard ratio (aHR; 0.33, 95% CI 0.16–0.71, $P = 0.004$) for the interaction between relapses and DMT initiation during follow-up. This finding suggests

that in people with PPMS who experience relapses, initiation of any DMT significantly reduces the risk of becoming wheelchair dependent.

This primary analysis was supported by multiple secondary analyses. Though not powered to detect differences between the types of DMT that were used, the point estimates for the aHRs suggest that higher-efficacy DMT may have a larger effect on progression than moderate-efficacy treatments in people with relapsing PPMS (higher efficacy: aHR 0.32; moderate efficacy: aHR 0.41). Further analyses included the duration of DMT use and an assessment of a subgroup of participants in whom MRI inflammatory disease activity (new T2 or gadolinium-enhancing lesions) could be collected as a marker of ongoing neuroinflammation. Both such models supported the primary result, again finding a significant interaction between DMT use and the presence of inflammatory disease activity for the outcome of reaching EDSS 7.0.

Strengths of the study include the robust end point of time to EDSS 7.0 and the long duration of follow-up. However, the sample size, following exclusions, was relatively modest for a registry study. In addition, as is implicit in such observational studies, residual bias between the propensity-matched groups cannot be excluded.

The new data, together with previous findings from RCTs and observational studies, are building a strong evidence base for the efficacy of immunomodulatory DMT in people with progressive MS who have evidence of active inflammatory disease[3,5,8,9]. Individuals with active PPMS should be considered for ocrelizumab treatment, where available. If resources were constrained or specific contraindications prevent ocrelizumab use, the data from this study would support the use of other high-efficacy DMTs. Importantly, however, we still largely lack disease-modifying treatments for people with inactive forms of progressive MS, which remains a major barrier to overcome in MS therapeutics. Large registry studies have

shown promise in identifying non-immunomodulatory treatments such as statins, which might reduce mortality in people with MS[10]. Further propensity-matched cohorts focusing on people with inactive progressive MS could identify further emerging treatments; potential candidates include metformin and pioglitazone, which are commonly used to treat diabetes mellitus[11,12]. Ultimately, however, as with ocrelizumab, the rigour of an RCT will be required before clinical practice can be changed.

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Competing interests

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Box 1 | Study inclusion criteria

The following criteria were used to select participants for the Portaccio et al. study[9].

Data availability and disease characteristics

- Diagnosis of primary progressive multiple sclerosis according to the 2010 McDonald Criteria.
- EDSS score <7.0 at study entry.
- Not receiving disease-modifying treatment at the time of the first recorded visit.
- At least three EDSS evaluations.
- At least 3 years of follow-up.
- Complete minimum data set.

Additional requirements based on the ORATORIO trial inclusion criteria

- Baseline functional systems pyramidal score (a subcomponent of the EDSS) ≥2.
- Age at onset: >18 years.
- EDSS score ≥5.5 with disease duration ≤15 years, or EDSS between 3.0 and 5.0 with disease duration ≤10 years.

EDSS, expanded disability status scale.