



In the clinic

Ocrelizumab for primary progressive multiple sclerosis

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For NICE guidance on ocrelizumab for primary progressive multiple sclerosis see <https://www.nice.org.uk/guidance/TA585>

For the ORATORIO trial see *N Engl J Med* 2017; **376**: 209–20

For NICE guidance on ocrelizumab for treatment of relapsing remitting multiple sclerosis see <https://www.nice.org.uk/guidance/ta533>

For the MS Trust survey see *Value Health* 2007; **10**: 54–60

On June 12, 2019, the UK National Institute for Health and Care Excellence (NICE) published guidance that recommends ocrelizumab, within its marketing authorisation, as an option for the treatment of patients with early primary progressive multiple sclerosis with imaging features characteristic of inflammatory activity in adults. Ocrelizumab is recommended only if Roche (Welwyn Garden City, UK) provides it according to the commercial arrangement with NHS England.

Ocrelizumab is an intravenous recombinant humanised anti-CD20 monoclonal antibody. Roche submitted evidence for clinical and cost-effectiveness, which an evidence review group critiqued. An independent appraisal committee met three times to develop guidance. Clinical experts and representatives from patients' organisations attended the first meeting. The committee knew that, other than ocrelizumab, there were no licensed disease-modifying treatments for primary progressive multiple sclerosis. In line with the anticipated marketing authorisation, the population described in NICE's scope of the appraisal covered all adults with primary progressive multiple sclerosis. The European Medicines Agency (EMA) ultimately granted marketing authorisation only for adults with early—in terms of disease duration and level of disability—primary progressive multiple sclerosis with imaging characteristics of inflammation. As NICE appraises a drug only within the marketing authorisation, the company limited its submission to this group. The committee concluded that ocrelizumab could increase demand for MRI scans.

To prove efficacy, the company presented findings from ORATORIO, a double-blind placebo-controlled trial of 732 people. The committee noted that the EMA defined early disease based on ORATORIO: an expanded disability

status scale (EDSS) score from 3.0 to 6.5, and a time since symptom onset of <15 years for EDSS scores >5.0 or <10 years for EDSS scores ≤5.0. The clinical experts considered this too long for early disease, but could not provide an alternative accepted definition. The company provided a post-hoc subgroup analysis of people in ORATORIO with gadolinium-enhancing T1 lesions at screening or baseline, or with new T2 lesions between screening and baseline; the clinical experts considered that this group of patients met accepted definitions. The committee concluded that the definition of early disease and the ORATORIO's MRI-active subgroup were appropriate.

The primary endpoint in ORATORIO was time to disability progression confirmed after 12 weeks (confirmed disability progression, CDP-12). Time to disability progression confirmed after 24 weeks (CDP-24) was a secondary endpoint. In line with previous appraisals for relapsing remitting multiple sclerosis, and considering comments from clinicians, the committee preferred analyses using CDP-24. At the second meeting, the company provided estimates of treatment effectiveness from an ongoing open-label extension of ORATORIO, during which time patients randomised to placebo could switch to ocrelizumab, for which the company adjusted. The committee noted that disability progression is subjective and preferred effectiveness measures from ORATORIO's double-blind period, making adjustment for switching unnecessary.

To estimate cost effectiveness, the company developed a disease model based on EDSS. Initially, the company excluded costs, disutilities, and treatment effects associated with relapses, and excluded the risk of progressive multifocal leukoencephalopathy (PML). To inform the course of untreated disease, the company did

not use ORATORIO's placebo group, but instead chose a disease registry (MSBase), explaining that, compared with ORATORIO, the registry had more patients, followed for longer and, compared to registries used in previous NICE appraisals for relapsing remitting multiple sclerosis, had more people with primary progressive disease. The company acknowledged that the MSBase registry offers limited MRI data. The committee noted that ORATORIO did not provide data to inform transition probabilities between all EDSS states and concluded that using the MSBase registry was appropriate.

The company assumed in its original submission that the relative treatment effect of ocrelizumab did not diminish over time, which the evidence review group and committee considered implausible. The company then used ORATORIO's open-label extension period to model a reducing effect from 10 years, whereas the evidence review group modelled a reducing effect from 7 years; the committee concluded that the true value likely falls between the two. In addressing how long people take ocrelizumab, the committee noted that the company extrapolated data from people still on treatment at trial's end, but did not limit this extrapolation to the MRI-active subgroup, which generated an estimate that the clinical experts considered too long. The company assumed that people whose disease progressed to EDSS state 8.0 would stop ocrelizumab, but the committee was aware that the end of treatment was later than when people stop disease-modifying treatments in relapsing remitting multiple sclerosis and concluded that it could not support a different stopping rule.

To estimate health-related quality of life by EDSS state, the company used ORATORIO or, for states for which ORATORIO offered no data, the company used values specific to primary

progressive multiple sclerosis from the MS Trust survey which the committee accepted. Initially, the company decreased utility in each EDSS state for upper limb dysfunction and clinically meaningful fatigue. The committee noted that these symptoms were among 17 exploratory ORATORIO end points, knew of regulatory principles which deem results only from planned analyses to be confirmatory, knew that appraisals for relapsing remitting multiple sclerosis had not used symptom-specific utility decrements, and heard from the clinical experts that upper limb dysfunction and fatigue are equally important for people with relapsing remitting multiple sclerosis.

The committee considered the company's third version of its cost-effectiveness estimates of ocrelizumab compared with best supportive care incorporating an updated (confidential) commercial arrangement. The company's revised model included a treatment effect diminishing from 7 or from 10 years, and the committee's preferred assumptions: costs, disutilities and a treatment effect associated with relapses; the risk of PML; CDP-24 to estimate treatment effect; data from ORATORIO's double-blind period to estimate treatment effect; and no separate disutilities for fatigue and upper limb dysfunction. The committee acknowledged remaining uncertainties related to the long-term

effect and treatment duration, and discussed unmet need. It concluded that ocrelizumab, with the commercial arrangement, was clinically effective and cost effective for treating early primary progressive multiple sclerosis with imaging features characteristic of inflammatory activity in adults.

We declare no competing interests.

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Insight

The neurology of the Cuban "sonic attacks"

Allegations of "sonic attacks" on 21 US embassy staff members in Cuba first made headlines in 2017. Embassy personnel described hearing intense, mostly high-pitched sounds, often combined with pressure-like or vibratory sensations, and experiencing persistent neurological symptoms afterwards. Speculations about the origin of these symptoms have ranged from clandestine operations to mass hysteria. The medical debate about the nature of the ensuing neurological disorder has been similarly polarised.

The symptoms should be familiar to every neurologist: headache, poor concentration and memory, dizziness, eye strain, tinnitus, sleep disturbance, etc. This set of symptoms can sometimes develop following a concussion, and a report concluded that some form of mild brain injury must have been inflicted. Others have suggested that mass psychogenic illness is a more probable cause of unexplained neurological symptoms in a close-knit social group. Neither hypothesis—brain damage or mass hysteria—is sufficiently supported by clinical evidence. Another hypothesis is that the symptoms correspond to a chronic functional disorder following acute sensory discomfort. Our prime motivation for making this point is not our confidence in having the right diagnosis (we have not seen the patients), but rather our concern at the widespread misunderstanding of functional disorders in the medical community. Functional neurological disorders are very common, accounting for about one in every six new neurology referrals. They comprise a range of disabling conditions with clinical signs

that seem incongruent with pathophysiological disease. But purely psychological models for functional disorders have given way to models that integrate psychological and neuroscience perspectives. Alterations in brain functioning are precipitated by unpleasant sensory experiences, which are distorted through overly precise attention and symptom expectations. Psychological factors of underlying trauma might increase individual risk but, much like smoking for risk of stroke, these factors are not essential to the diagnosis.

The functional disorder persistent postural-perceptual dizziness (PPPD) is the second most common cause of dizziness seen in tertiary centres. It usually develops after an acute vestibular disorder, but can also be triggered by a panic attack or mild head injury. Acute dizziness, of any cause, prompts automatic changes in balance control, such as stiffening of gait and increased body awareness. Dizziness can then persist in a cycle of maladaptation. PPPD has characteristic diagnostic features, including typical exacerbating factors of upright posture, active or passive motion, and exposure to moving or complex visual stimuli, which seem reminiscent of the brief description of dizziness in the embassy personnel: "symptoms were exacerbated by walking quickly, tasks involving head movements, complex visual environments, or in some cases while simply standing still." Of note, PPPD has no psychological diagnostic requirements.

The embassy workers also reported headache, light-sensitivity, and sleep disturbances, as well as cognitive



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For the **original report on "sonic attacks"** see *JAMA* 2018; **319**: 1125–33

For **further discussion on the origin of symptoms** see *JAMA* 2018; **320**: 602–3

For an **update on functional neurological disorders** see *JAMA Neurol* 2018; **75**: 1132–41

For a **review of persistent postural-perceptual dizziness** see *Pract Neurol* 2018; **18**: 5–13

For more on **functional disorders** see Hallett M, Stone J, Carson A, eds. *Functional Neurologic Disorders*. Oxford, UK: Elsevier, 2016