Feast or famine in multiple sclerosis therapeutics

Over the past 30 years, the number of drugs approved for multiple sclerosis has gone from zero to more than 15, with several dosing variations and generic versions. Despite this great progress, current multiple sclerosis treatments seem to predominantly benefit the inflammatory lesion activity that underlies relapsing multiple sclerosis, leaving the progressive aspects (ie, gradual disability worsening without clinical relapses) mostly unabated. Siponimod and ocrelizumab are two agents with regulatory approval for progressive forms of multiple sclerosis (primary progressive and secondary progressive multiple sclerosis); these drugs provide the most benefit to patients with clinical relapses or disease activity on MRI. As a result, when US and European regulators recommended approval of siponimod for secondary progressive multiple sclerosis, they restricted its use to patients with active disease. Treatments for patients with progressive multiple sclerosis who do not have active disease are scarce.

In The Lancet Neurology, Jeremy Chataway and colleagues report their attempt to address this problem with a multiarm phase 2b trial in patients with secondary progressive multiple sclerosis, the Multiple Sclerosis Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART). The authors selected three experimental drugs (amiloride, fluoroxetine, and riluzole) for MS-SMART that were identified by extensive systematic review of 532 treatment candidates. These drugs target axonal pathobiology and neuroprotection, and have extensive evidence of use in humans with established safety profiles, so were ready for trial testing in progressive multiple sclerosis. The primary outcome was whole-brain atrophy and this endpoint is commonly used in progressive multiple sclerosis phase 2 trials. The study achieved target enrolment, and retention was excellent at 88% over 96 weeks. Despite rigorous theoretical grounding, sound experimental design, and admirable execution, MS-SMART did not achieve its primary outcome. None of the three tested drugs slowed progression of whole-brain atrophy compared with placebo.

These disappointing results raise an obvious question: why was a promising treatment not identified to carry forward into phase 3 trials? The answer is unclear, but several possibilities merit consideration. The systematic review process of potential treatments seems inadequate. The true pathophysiology of progressive multiple sclerosis remains unknown, and with this paucity of knowledge, accurate drug selection is compromised. In progressive multiple sclerosis, leucocyte infiltration into the CNS is less prominent than in relapsing multiple sclerosis and is replaced by a shift to innate immune mechanisms sequestered behind the blood–brain barrier, mitochondrial dysfunction, metabolic dysregulation secondary to chronic demyelination, and possibly a magnified effect of normal aging and ongoing comorbid conditions. Researchers need to re-double their efforts to identify the true mechanisms driving multiple sclerosis progression, which will then enable effective drug selection. This lesson probably applies across the spectrum of neurodegenerative disorders, including Alzheimer’s disease and Parkinson’s disease.

An increased mechanistic understanding of neurodegenerative disorders will enable validation of biological target engagement during trials. Without confirming that the investigative drug engaged with its molecular or cellular target, it is difficult to select the optimum drug dose. In relapsing multiple sclerosis, biological target engagement has been unnecessary because the presence of new lesions on MRI is a sensitive treatment response biomarker, regardless of the intended biological target. Biomarkers have a variety of uses in clinical medicine, including pharmacologic responses to therapeutic interventions. Target engagement becomes of greater importance in progressive multiple sclerosis because no biomarker outcomes have phase 3 trial validation. Whole-brain atrophy has inherent limitations, including day-to-day biological variability, slow dynamic change over time, limited scalar granularity as a full-brain metric, and technical challenges when MRI acquisition and equipment change over the course of a trial. Better phase 2 trial metrics will improve trial efficiency, allowing fewer patients to be enrolled and shortening trial duration. Magnetisation transfer imaging, cortical atrophy, and slowly expanding lesions are example metrics that show promise to be more sensitive than whole-brain atrophy, although further validation studies are needed. Fluid-based treatment response biomarkers also are being sought, with neurofilament-light emerging as a leading candidate.
Issues important to the design of stroke recovery trials

Stroke recovery trials aim to improve outcomes by promoting repair in surviving neural systems, by contrast with acute reperfusion trials, which aim to salvage threatened tissue by targeting clots and arteries. Several drugs, biologicals, devices, and behavioural training paradigms have shown promise in preclinical studies targeting repair.1

One such recovery-based therapy was examined in the RESTORE BRAIN study.2 In The Lancet Neurology, Hugues Chabriat and colleagues evaluated the safety and efficacy of S44819, a GABAA α5 receptor antagonist, administered as 150 mg or 300 mg orally twice a day over 90 days starting 3–8 days post-stroke, in a placebo-controlled trial of 585 patients. S44819 was safe, but neither dose differed from placebo in the primary endpoint, modified Rankin Scale (mRS) score at day 90, or in the secondary endpoints. The authors are to be congratulated for carefully completing a large trial in less than 2 years.

What can we learn from this trial? Several issues emerge related to clinical translation and trial design, particularly with respect to endpoints and biomarkers.

In preclinical studies,2,4 S44819 improved motor function (according to Rotarod, tightrope, or single pellet reaching tests) and spatial memory (Barnes maze test). The primary endpoint in the RESTORE BRAIN trial, however, was the mRS, a measure of global disability that is affected by several behavioural and psychosocial factors. The choice of mRS introduced several limitations.

First, the relationship between the mRS score and the preclinical measures that showed drug efficacy is unclear. Initial translation to human studies might benefit from including endpoints closely aligned with behaviours that were improved by treatment in animals. In particular, preclinical endpoints tend to be impairment-based, suggesting utility of impairment (rather than global disability) scales in initial human translational studies. Second, mRS has limited granularity, with only six levels...