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Multiple sclerosis in 2018: new therapies and biomarkers

2018 has been a year of substantial progress in multiple sclerosis research, with breakthroughs in experimental medicine and translational research. Advances have ranged from successful clinical trials to new reports of promising biomarkers and improved understanding of the pathophysiology of multiple sclerosis.

More than a dozen disease-modifying therapies exist for relapsing-remitting multiple sclerosis, but only one therapy has been approved by regulators to slow progression in primary progressive multiple sclerosis (ocrelizumab), and no therapies have been approved with that specific indication in secondary progressive multiple sclerosis. Ibudilast, a phosphodiesterase inhibitor that crosses the blood–brain barrier, reduced the rate of brain atrophy by about 48% compared with placebo in the phase 2 SPRINT-MS randomised trial[1] of 255 patients with progressive multiple sclerosis, thereby leading the way to a phase 3 trial. Beyond the promise of this new therapy, this trial is important for a few reasons: it was a multicentre trial that provided data from five advanced imaging metrics (transverse and longitudinal diffusivity in the corticospinal tract, magnetisation transfer ratio in normal-appearing tissue, thickness of the retinal nerve fibre layer, and cortical thickness), demonstrating that it is feasible to include advanced methods in trials to detect the effect of experimental therapies on brain microstructure. Furthermore, SPRINT-MS[1] also showed the potential for drug repurposing in multiple sclerosis (ie, the application of a drug that is already used for a different indication), because ibudilast is used in Asia for treatment of patients with asthma or post-stroke vertigo. Drug repurposing is an attractive strategy that could lead to the discovery of an effective treatment sooner and at a lower cost than de novo drug development. About half of the patients enrolled in the SPRINT-MS trial[1] had primary progressive multiple sclerosis, confirming that secondary progressive and primary progressive multiple sclerosis can be studied together because they share more similarities than differences. Another notable result was that the rate of brain atrophy in the placebo group was lower than that reported in observational studies and in other trials of progressive multiple sclerosis, making it difficult to generalise this finding to the general population.

A disease-modifying treatment that has followed a standard development pathway is siponimod, a selective sphingosine-1-phosphate receptor modulator that inhibits the egress of lymphocytes from lymph nodes and crosses the blood–brain barrier. Siponimod induced a 21% reduction of the risk of 3-month confirmed disability progression compared with placebo in the phase 3 EXPAND study[2] of 1651 patients with secondary progressive multiple sclerosis. The safety profile was similar to that of other sphingosine-1-phosphate receptor modulators, and the dose titration during the first 6 days of treatment mitigated the risk of cardiac adverse events associated with these drugs. The patient characteristics were as expected for secondary progressive multiple sclerosis, but 21% of patients showed gadolinium-enhancing lesions on MRI at baseline and about a third had a relapse in the 2 years before screening, suggesting that some patients had active inflammatory disease. The trial was an event-driven and exposure-driven study, so median exposure to the drug was 18 months (range 0–37 months), which is shorter than other trials in secondary progressive multiple sclerosis, after which the open-label extension of the trial commenced. Subgroup analyses showed that patients with higher disease activity, younger age, lower disability, and shorter disease duration were more likely to benefit from siponimod than patients with the opposite characteristics. Whether the

licensing indication will be restricted to specific groups of patients is unknown, but siponimod might be the first disease-modifying therapy to receive marketing approval for slowing progression in secondary progressive multiple sclerosis.

2018 has also been an important year for paediatric multiple sclerosis, because the first phase 3 clinical trial in this population was published.[3] Treatment regimens in paediatric multiple sclerosis are centre specific and based predominantly on adult protocols; data on the alleged efficacy and safety of disease-modifying therapies in paediatric patients are derived from retrospective and open-label studies rather than randomised, controlled trials. In the PARADIGMS randomised trial[3] of 215 patients aged 10–17 years, fingolimod (another sphingosine-1-phosphate receptor modulator licensed for adults with relapsing-remitting multiple sclerosis) was associated with 82% lower rate of relapses compared with intramuscular interferon beta-1a over a median of 1·61 years. Notably, both groups had a high frequency of T2 new or enlarging lesions (9·27 lesions per year in the interferon beta-1a group and 4·39 lesions per year in the fingolimod group), which is higher than the rate usually observed in adults, indicating a high inflammatory activity in children with multiple sclerosis. An ongoing open-label 5-year extension involving the same population is testing the durability and safety of fingolimod in paediatric multiple sclerosis.

In addition to the progress in treatments for progressive multiple sclerosis and paediatric multiple sclerosis in 2018, a large amount of work has focused on developing new biomarkers for neurodegeneration. Particularly notable are the studies on imaging biomarkers and serum neurofilaments. Whole-brain atrophy on MRI is driven mainly by grey matter atrophy, which is not uniform across the brain, but involves some regions more extensively than others. A large longitudinal study of 1417 patients with multiple sclerosis[4] from the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) network showed that the sequence in which grey matter regions became atrophic on MRI was similar across multiple sclerosis subtypes, and atrophy spread to involve more regions over time. The progression of atrophy through different stages (figure; based on the number of grey matter regions affected) was associated with disability accumulation. This marker of progression could be used at the individual level for automatic assessment of patients and for monitoring the course of multiple sclerosis, with the hope of enabling personalised treatment choices.

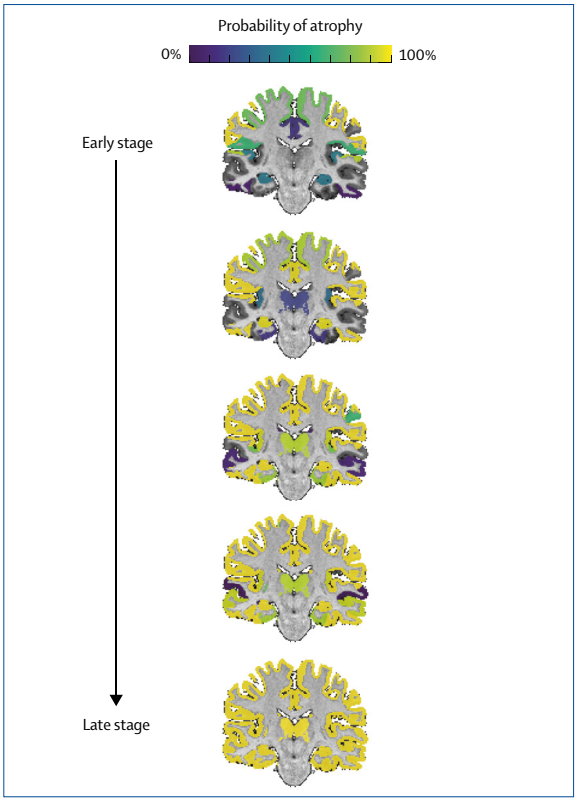

Figure: **Progression of grey matter atrophy in multiple sclerosis**
Colour-coded probability of regional grey matter atrophy in brains of patients with multiple sclerosis is overlaid on coronal MRI scans. Few cortical grey matter lesions are affected in the early stage of multiple sclerosis, whereas extensive and widespread atrophy involving the whole cortex and the deep grey matter occurs in the latest stage. Courtesy of Arman Eshaghi (University College London, London, UK).

Neurofilament light chain, a constituent of the neuronal cytoskeleton, is a marker of neuroaxonal damage in many neurodegenerative diseases, such as motor neuron disease[5] and Alzheimer's disease.[6] It was originally measured in CSF, but the advent of methods that measure it in the serum has made it a more attractive biomarker. A large longitudinal study of people with relapsing-remitting and people with progressive multiple sclerosis[7] showed that higher concentrations of neurofilament light chain at baseline were associated with disability worsening over time and predicted brain and spinal cord atrophy. Neurofilament light chain seems to reflect concurrent changes in neuronal structure and is sensitive to treatment,[8] raising the possibility that, once a standardised, robust, and widely accessible assay is validated and normative values of neurofilaments across

age groups are provided, such measurements might be used for individual patient monitoring.

Overall, the findings from multiple sclerosis research in 2018 hold great promise for the treatment of progressive multiple sclerosis and for the availability of new biomarkers to monitor disease progression.

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New therapies for neuromuscular diseases in 2018

Advances in treatments for neuromuscular diseases, particularly those with a genetic basis, have been a key story this year, illustrated by treatment of the rare condition hereditary transthyretin amyloidosis. This progressive, multisystemic, autosomal dominant disorder leads to death on average within 3–15 years of symptom onset and is caused by mutations in the *TTR* gene that trigger deposition of misfolded transthyretin protein throughout the body. Sensory, motor, and autonomic polyneuropathy is a major feature of the disease and a substantial determinant of disability and quality of life. Two successful double-blind, randomised, placebo-controlled phase 3 trials, APOLLO[1] and NEURO-TTR,[2] used different gene therapy approaches to block the production of transthyretin in the liver, which is the predominant source of this protein, and illustrate different paradigms for the treatment of genetic disease. Patisiran, administered intravenously in APOLLO, is a double-stranded siRNA that targets *TTR* mRNA for cleavage and reduces the levels of both mutant and wild-type transthyretin; the drug, encapsulated in a lipid nanoparticle, precisely targets *TTR* mRNA in hepatocytes. Inotersen, delivered subcutaneously in NEURO-TTR, is a 2′-O-methoxyethyl-modified antisense oligonucleotide that inhibits the hepatic production of transthyretin protein by binding to *TTR* mRNA. Both treatments resulted in significant improvements in neuropathy, as measured by the modified Neuropathy Impairment Score+7 (difference of −34·0 points for patisiran [95% CI −39·9 to −28·1; p<0·001]; −19·7 points for inotersen [−26·4 to −13·0; p<0·001]) and quality of life scores (difference of −21·1 points for patisiran [95% CI, −27·2 to −15·0; p<0·001]; −11·7 points for inotersen [−18·3 to −5·1; p<0·001]) compared with placebo.[1,2] On the basis of these results, disease progression was considered to be halted or reversed. Mild-to-moderate adverse events were frequent with patisiran, but inotersen caused more frequent serious adverse effects, including thrombocytopenia in more than 50% of patients (with one resultant death from an intracranial haemorrhage in NEURO-TTR) and glomerulonephritis in 3% of patients; treatment with inotersen will therefore require enhanced monitoring. It remains to be seen whether these drugs will be efficacious for cardiomyopathy associated with hereditary transthyretin amyloidosis, and long-term follow-up is needed. Patisiran is now the first RNA-interfering therapy to be approved by the US Food and Drug Administration.

Conceptually, it would seem most appealing to edit the patient's genome itself to treat genetic disorders. An exciting development in the laboratory, which offers hope for the future treatment of many genetic neuromuscular and neurodegenerative diseases, is somatic cell mutagenesis using enzymatic clustered regularly spaced short palindromic repeats (CRISPR)-Cas9 gene editing, a type of so-called magic bullet that can precisely edit