

Multiple sclerosis in 2018: new therapies and biomarkers

Olga Ciccarelli
UCL Queen Square Institute of Neurology
London
o.ciccarelli@ucl.ac.uk

2018 has been a year of substantial progress in multiple sclerosis, 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.

There are more than a dozen disease-modifying therapies 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% when compared to placebo in the phase 2 SPRINT-MS randomised trial of 255 patients with progressive multiple sclerosis,¹ thereby leading the way to a phase 3 trial. Beyond the promise of this therapy, this trial is important for a few reasons. This was a multicentre trial that provided data from five advanced imaging metrics (transverse and longitudinal diffusivity in the cortico-spinal tract, magnetization transfer ratio in the normal-appearing tissue, 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. This trial also showed the potential of drug repurposing in multiple sclerosis (i.e., the application of a drug that is already used for a different indication), as ibudilast is used in Asia for asthma and 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 ibudilast trial had primary progressive multiple sclerosis, confirming that secondary progressive and primary progressive multiple sclerosis can be studied together since they share more similarities than differences. Finally, the rate of brain atrophy in the placebo group of this trial was lower than that previously reported in observational studies and in other trials of progressive MS, making it difficult to generalise this finding to the general population.

A disease-modifying treatment that 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, which included 1651 patients with secondary progressive multiple sclerosis.² The safety profile was similar to that of other sphingosine-1-phosphate receptor modulators, and the dose titration at the beginning of the treatment was useful to reduce 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 one third had a relapse in the two years before screening, suggesting that some patients had

active inflammatory disease. The trial was an event- and exposure-driven study, so patients were treated only for a median of 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 were 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, as the first phase 3 clinical trial was published.³ Current 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, and not from randomised, controlled trials. In the PARADIGMS randomised trial of 215 paediatric patients, fingolimod (another sphingosine-1-phosphate receptor modulator licensed for adults with relapsing-remitting multiple sclerosis) was associated with 82% lower rate of relapses when compared with intramuscular interferon beta-1a over a median of 1.61 years.³ Interestingly, there was a high frequency of T2 new or enlarging lesions in both the placebo arm (9.23 per annum) and treated arm (4.39), which is higher than the rate usually observed in adults, indicating a high inflammatory activity in children with MS. An open-label 5-year extension involving the same population is currently testing the durability and the safety of fingolimod in paediatric multiple sclerosis.

Beside the progress in treatments for people with progressive multiple sclerosis and children with multiple sclerosis, in 2018 a large amount of work focused on developing new biomarkers for neurodegeneration. Particularly notable are the studies on imaging biomarkers and serum neurofilaments. Whole brain atrophy on MRI is mainly driven by grey matter atrophy, which is not uniform across the brain, but involves some regions more extensively than others. A large study⁴ 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 (based on the number of grey matter regions affected) was associated with disability accumulation (**Figure**). The promise is that this marker of progression will be used at the individual level for automatic assessment of patients and the progress of their multiple sclerosis, with the hope of enabling personalised treatment choices.

Neurofilament light chain, a constituent of the neuronal cytoskeleton, is a marker of neuroaxonal damage in many neurodegenerative diseases, such as motor neuron disease⁵ and Alzheimer's disease⁶. 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 in relapsing-remitting and progressive multiple sclerosis⁷ showed that higher levels of neurofilament light protein 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 treatment⁸, raising the

possibility that, once a standardised, robust and widely accessible assay is validated, and normative values of neurofilaments across age groups are provided, neurofilament measurements might be used for individual patient monitoring.

Multiple sclerosis research in 2018 holds great promise for the treatment of progressive multiple sclerosis and for the availability of new biomarkers to monitor multiple sclerosis in the individuals, which hopefully will be fulfilled in the near future.

Conflict of interest:

OC is a NIHR Research Professor. She is supported by National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC). Dr. Ciccarelli reports grants from UK MS Society, National MS Society, NIHR UCLH, BRC, Progressive MS Alliance, Bioclinica & GE Neuro, EU-H2020, Spinal Cord Research Foundation, and Rosetrees Trust; personal fees from Novartis, Teva, Roche, and Merck, outside the submitted work; she receives an honorarium from Neurology.

REFERENCES:

1. Fox RJ, Coffey CS, Conwit R, Cudkovic ME, Gleason T, Goodman A, Klawiter EC, Matsuda K, McGovern M, Naismith RT, Ashokkumar A, Barnes J, Ecklund D, Klingner E, Koeppe M, Long JD, Natarajan S, Thornell B, Yankey J, Bermel RA, Debbins JP, Huang X, Jagodnik P, Lowe MJ, Nakamura K, Narayanan S, Sakaie KE, Thoomukuntla B, Zhou X, Krieger S, Alvarez E, Apperson M, Bashir K, Cohen BA, Coyle PK, Delgado S, Dewitt LD, Flores A, Giesser BS, Goldman MD, Jubelt B, Lava N, Lynch SG, Moses H, Ontaneda D, Perumal JS, Racke M, Repovic P, Riley CS, Severson C, Shinnar S, Suski V, Weinstock-Guttman B, Yadav V, Zabeti A; NN102/SPRINT-MS Trial Investigators. Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis. *N Engl J Med*. 2018 Aug 30;379(9):846-855. doi: 10.1056/NEJMoa1803583.
2. Kappos L, Bar-Or A, Cree BAC, Fox RJ, Giovannoni G, Gold R, Vermersch P, Arnold DL, Arnould S, Scherz T, Wolf C, Wallström E, Dahlke F; EXPAND Clinical Investigators. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet*. 2018 Mar 31;391(10127):1263-1273.
3. Chitnis T, Arnold DL, Banwell B, Brück W, Ghezzi A, Giovannoni G, Greenberg B, Krupp L, Rostásy K, Tardieu M, Waubant E, Wolinsky JS, Bar-Or A, Stites T, Chen Y, Putzki N, Merschhemke M, Gärtner J; PARADIGMS Study Group. Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis. *N Engl J Med*. 2018 Sep 13;379(11):1017-1027.
4. Eshaghi A, Marinescu RV, Young AL, Firth NC, Prados F, Jorge Cardoso M, Tur C, De Angelis F, Cawley N, Brownlee WJ, De Stefano N, Laura Stromillo M, Battaglini M, Ruggieri S, Gasperini C, Filippi M, Rocca MA, Rovira A, Sastre-Garriga J, Geurts JGG, Vrenken H, Wottschel V, Leurs CE, Uitdehaag B, Pirpamer L, Enzinger C, Ourselin S,

Gandini Wheeler-Kingshott CA, Chard D, Thompson AJ, Barkhof F, Alexander DC, Ciccarelli O. Progression of regional grey matter atrophy in multiple sclerosis. *Brain*. 2018 Jun 1;141(6):1665-1677. doi: 10.1093/brain/awy088.

5. Feneberg E, Oeckl P, Steinacker P, Verde F, Barro C, Van Damme P, Gray E, Grosskreutz J, Jardel C, Kuhle J, Koerner S, Lamari F, Amador MDM, Mayer B, Morelli C, Muckova P, Petri S, Poesen K, Raaphorst J, Salachas F, Silani V, Stubendorff B, Turner MR, Verbeek MM, Weishaupt JH, Weydt P, Ludolph AC, Otto M. [Multicenter evaluation of neurofilaments in early symptom onset amyotrophic lateral sclerosis](#). *Neurology*. 2018 Jan 2;90(1):e22-e30. doi: 10.1212/WNL.0000000000004761.
6. Mattsson N, Andreasson U, Zetterberg H, Blennow K; Alzheimer's Disease Neuroimaging Initiative. Association of Plasma Neurofilament Light With Neurodegeneration in Patients With Alzheimer Disease. *JAMA Neurol*. 2017 May 1;74(5):557-566. doi: 10.1001/jamaneurol.2016.6117.
7. Kuhle J, Disanto G, Lorscheider J, Stites T, Chen Y, Dahlke F, Francis G, Shrinivasan A, Radue EW, Giovannoni G, Kappos L. Fingolimod and CSF neurofilament light chain levels in relapsing-remitting multiple sclerosis. *Neurology*. 2015 Apr 21;84(16):1639-43. doi: 10.1212/WNL.0000000000001491.
8. Barro C, Benkert P, Disanto G, Tsagkas C, Amann M, Naegelin Y, Leppert D, Gobbi C, Granziera C, Yaldizli Ö, Michalak Z, Wuerfel J, Kappos L, Parmar K, Kuhle J. Serum neurofilament as a predictor of disease worsening and brain and spinal cord atrophy in multiple sclerosis. *Brain*. 2018 May 30. doi: 10.1093/brain/awy154.

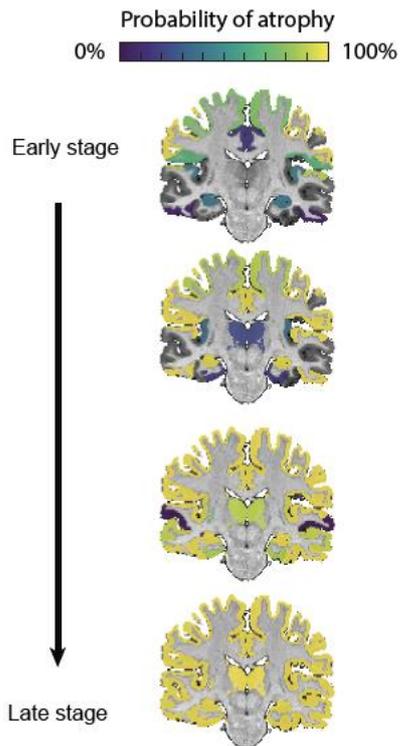


Figure 1: Relationship between grey matter atrophy progression and disability worsening.

The probability of regional grey matter atrophy in the brain of patients with MS is overlaid only coronal MRI scans and is colour coded, so that brighter and more yellow colours indicate a high probability of atrophy, while darker colours indicate a low probability of atrophy. A few cortical grey matter lesions are affected in the early stage of multiple sclerosis, while extensive and widespread atrophy involving the whole cortex and the deep grey matter is seen in the latest stage. *Courtesy of Arman Eshaghi, UCL.*