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MILESTONE 9

Progressive and aggressive MS — new frontiers emerge

The huge progress made in the treatment of relapsing–remitting multiple sclerosis (RRMS) in the past 25 years has not been replicated for progressive forms of multiple sclerosis (MS) or for aggressive MS that does not respond to disease-modifying therapies (DMTs). However, progress has been made in the past 2–3 years, making these areas the new frontiers.

Progressive MS is characterized by accumulation of disability without relapses. In primary progressive MS (PPMS), this disease course occurs from the onset, whereas in secondary progressive MS (SPMS) this course follows a relapsing–remitting phase.

After years of failure to develop treatments for progressive MS, a major breakthrough was seen in 2017 when ocrelizumab was approved as the first treatment for PPMS.

The approval of ocrelizumab for PPMS was based on results of the ORATORIO trial, published in 2017. In this trial, 732 patients with PPMS received either ocrelizumab or placebo every 24 weeks for at least 120 weeks. Relative to placebo, ocrelizumab reduced 12-week and 24-week disability progression and slowed brain atrophy. Ocrelizumab also reduced brain lesion volume relative to baseline. Given that ocrelizumab depletes B cells (MILESTONE 8), its efficacy in PPMS implicates B cells in the pathophysiology of progressive disease, forming the basis for testing and development of other B cell-targeted therapy in this context.

A lack of therapeutic options in SPMS also looks likely to end following the EXPAND study, a phase III trial of siponimod. Siponimod is a sphingosine 1-phosphate (S1P) receptor inhibitor that acts similarly to fingolimod (MILESTONE 4) in preventing egress of lymphocytes from lymphoid tissue and reducing migration of peripheral lymphocytes into the CNS. In EXPAND, 1,645 patients with SPMS were randomly assigned to receive 2 mg of oral siponimod or placebo once per day for up to 3 years. Treatment with siponimod led to a 21% reduction in the relative risk of 3-month confirmed disability progression. The safety profile was good, so the trial suggests that siponimod could be a useful treatment in SPMS.

Aggressive MS is not well defined, but can be described as highly active disease that causes early and rapid progression of disability. One treatment with potential in aggressive MS and progressive MS is autologous haematopoietic stem cell transplantation (aHSCT).

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This procedure, first developed to treat haematological malignancies, involves extraction of haematopoietic stem cells (HSCs) from the patient, followed by suppression or ablation of the immune system and subsequent replacement of the HSCs to enable immune reconstitution. Safety concerns have meant that aHSCT has only been used as a rescue therapy after other options have been exhausted. However, safety has improved in the latest studies, and the efficacy is striking.

In a study published in 2016, immunoablation and aHSCT in 24 patients drastically affected MS disease activity. During follow-up (median 6.7 years), no patients had relapses and no new lesions were detected with MRI. One patient died, highlighting the remaining risks, but mortality was much lower than in many previous studies. Similarly, in the HALT-MS study published in 2017, high-dose immunosuppression followed by aHSCT in 24 patients resulted in freedom from disease activity in 70% of patients over a median follow-up period of 62 months. No unexpected adverse events were reported.

Finally, in a study of long-term outcomes, almost half of 281 patients who underwent aHSCT for MS were free of disease progression at 5 years. Mortality was again lower than in many previous studies, at 2.8%. Importantly, almost 80% of patients in this study had progressive MS.

Together, the trials in progressive and aggressive MS demonstrate the encouraging steps taken towards treatments for the most disabling forms of MS. These steps lay the foundations for a second 25 years of MS treatment that is as successful as the first.

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