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MULTIPLE SCLEROSIS

Immune reconstitution effective for MS

> “all inflammatory activity can be stopped following… reconstitution of a naïve immune system”

Complete immunoablation followed by autologous haematopoietic stem cell transplantation (aHSCT) stops progression of multiple sclerosis (MS), a recently published trial shows. The treatment had greater efficacy than any other available therapeutic approach to MS, and could offer a new way of tackling aggressive disease in some patients.

Immune system suppression and aHSCT for MS has previously produced promising results in short follow-up periods, but no treatment has prevented the disease from eventually re-emerging in some patients. In the new study, Harold Atkins and colleagues tested a more aggressive approach in 24 patients with aggressive disease and poor responses to treatment.

“Mark Freedman, myself and our collaborators wanted to investigate whether removing the immune system and reconstituting a naïve immune system would control MS,” he explains. “We adapted strategies that are used in aHSCT for malignancies and were most likely to achieve the goals of removing the autoreactive immune system and reconstituting a new immune system.”

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Before the treatment, haematopoietic stem cells were isolated from each patient for later transplantation. Aggressive chemotherapy with a combination of busulfan, cyclophosphamide and rabbit anti-thymocyte globulin was then used to ablate the immune system before haematopoietic stem cells were transplanted back into patients to reconstitute their immune systems.

One patient died as a result of the treatment, highlighting the risks of the approach, but efficacy in the other 23 patients was striking. Overall MS activity-free survival at 3 years after treatment was 69.6%, and over a follow-up period of up to 13 years (median 6.7 years), no patients experienced any relapses, and no gadolinium-enhancing lesions or new T2 lesions were detected. Rates of brain atrophy slowed to those expected with normal ageing.

“These findings are important, as they demonstrates that all inflammatory activity can be stopped following elimination of the autoreactive immune system and reconstitution of a naïve immune system,” says Atkins.

In addition, 70% of patients exhibited no further progression of disability after treatment, as assessed with the Extended Disability Status Scale (EDSS). Moreover, by 7.5 years after treatment, 40% of patients had improved EDSS scores that translated into dramatic functional recoveries, sufficient for some patients to return to work, get married and have children.

“This study shows the most profound suppression of inflammatory disease activity ever shown by any treatment in MS for a prolonged period,” says Paolo Muraro, head of the Clinical Neuroimmunology Group at the Division of Brain Sciences, Imperial College London, UK.

In many patients, the procedure led to a variety of adverse events, and the death of one patient raises safety concerns that have been voiced previously. According to Muraro, many of these events, such as fever, urinary tract infection and low blood cell counts, are expected and can be managed relatively easily.

“The more relevant risk is of organ toxicites from the cytotoxic chemotherapy and severe, antibiotic-resistant infections that can follow the complete immune suppression,” he says. “These complications of the treatment can be fatal, and treatment-related mortality is a critical factor to consider in the development of this therapeutic approach. Striking a balance between effectiveness and safety is key.”

For Atkins, Freedman and their team, their findings are proof that use of immunoablation and aHSCT provides a new way to treat highly active, aggressive MS, and they are looking to refine the use of this approach. “Future work will be directed at determining whether this treatment could be used in other patient groups and in mitigating the toxicity of the procedure,” Atkins says.

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ORIGINAL ARTICLE Atkins, H. L. *et al.* Immunoablation and autologous haematopoietic stem cell transplantation. *Lancet* http://dx.doi.org/10.1016/S0140-6736(16)30169-6 (2016)
FURTHER READING Dörr, J. Haematopoietic stem-cell transplantation for multiple sclerosis: what next? *Lancet* http://dx.doi.org/10.1016/S0140-6736(16)30377-4 (2016)