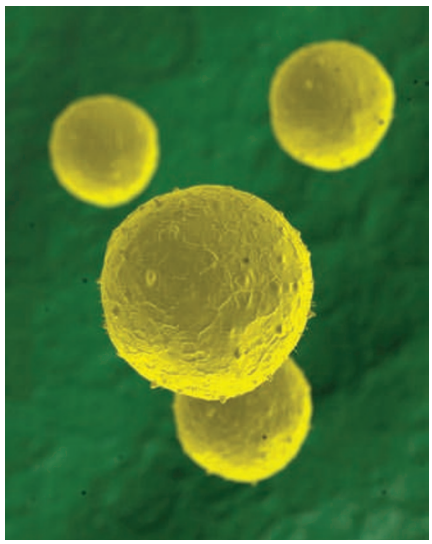
MULTIPLE SCLEROSIS

Stem cell transplants ameliorate neurological deficits in multiple sclerosis

Hematopoietic stem cell transplantation has been under investigation as a potential treatment for multiple sclerosis (MS) for over a decade, and several studies have indicated that this treatment can stabilize neurological disability in patients with this condition. Until now, however, little evidence has suggested that this treatment can reverse the disease process. In *The Lancet Neurology*, Richard Burt and colleagues at Northwestern University, Chicago, USA, report that autologous, non-myeloablative, hematopoietic stem cell transplantation can improve neurological deficits if performed during the relapsing–remitting phase of MS.

The goal of autologous hematopoietic stem cell transplantation is to eliminate autoreactive lymphocytes and replace them with self-tolerant ones, thereby 'resetting' the immune system and halting the autoimmune process. To date, this procedure has been performed mostly in patients with secondary progressive MS, in which the neurological deficits are attributable largely to axonal degeneration. Burt *et al.* surmised that this stage of the disease would be less amenable to immune-based therapies than the earlier relapsing–remitting phase, in which the predominant underlying mechanism is immune-mediated demyelination. This mechanism might provide an explanation for the limited benefits derived from this treatment approach in patients with secondary progressive MS.

Burt *et al.* recruited 21 patients (11 women and 10 men) with relapsing–remitting MS. The patients had clinically definite MS according to the Poser criteria, were aged between 18 and 55 years, and had failed to respond to interferon-β therapy over a period of at least 6 months. Participants received intravenous cyclophosphamide and subcutaneous filgrastim to mobilize their peripheral blood stem cells, which were subsequently collected by apheresis and cryopreserved. Before transplantation, the patients were conditioned with cyclophosphamide plus either alemtuzumab or rabbit antithymocyte globulin, and the stem cells were reinfused into the patients 36 h after completion of the cyclophosphamide treatment. Patients were assessed at baseline, at 6 months and 12 months after treatment, and annually thereafter. The primary outcome measures were progression-free survival and reversal of neurological disability 3 years after transplantation, and the patients were also assessed for the appearance of new brain lesions on MRI. Safety and tolerability of the treatment were additional important considerations.



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Burt and his colleagues monitored the patients for a mean period of 3 years. The rate of progression-free survival was 100%, and 19 of the 21 patients showed improvements on the Kurtzke expanded disability scale (EDSS), with 17 showing an increase of 1 point or more. EDSS scores in the remaining two patients were unchanged. The patients also reported improvements in quality of life. Five patients experienced relapses between 6 months and 12 months after treatment, and in three cases the relapses were associated with the appearance of new gadolinium-enhancing lesions on MRI. All patients who relapsed achieved remission after further immunosuppressive treatment. Five patients developed neutropenic fever, and one patient showed transient left-sided hypoesthesia, which was attributed to the filgrastim treatment.

The authors chose a non-myeloablative conditioning regimen to avoid the high mortality that had previously been reported in association with intense myeloablative regimens in patients with various autoimmune diseases, including MS. No patients died as a result of the transplantation procedure, and it was generally well tolerated. However, two patients developed immune thrombocytopenia, which was attributed to the use of alemtuzumab. As a consequence, this drug was replaced by antithymocyte globulin in patients who received transplants subsequently.

The results of the Burt *et al.* study indicate that autologous, non-myeloablative, hematopoietic stem cell transplantation can not only prevent disease progression in patients with relapsing–remitting MS, but can also initiate a reversal in the neurological deficits in a substantial proportion of patients. The authors propose that the next step will be to perform a randomized trial to determine whether this approach is superior to standard treatments for MS. In addition, the patients in the present study are still being evaluated to establish whether the transplants succeeded in resetting the immune system, or whether the procedure merely provided transient immune suppression.

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Original article Burt, R. K. *et al.* Autologous non-myeloablative haematopoietic stem cell transplantation in relapsing–remitting multiple sclerosis: a phase I/II study. *Lancet Neurol.* **8**, 244–253 (2009).