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ARTICLE IN BRIEF

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In a small trial, patients with relapsing MS who had an autologous hematopoietic stem cell transplant showed some improvements in neurological function.

Investigators at Northwestern University have successfully reversed the course of multiple sclerosis (MS) in 21 patients by resetting the patient's immune system through autologous stem cell transplantation, using their own progenitor cells to reconstitute normal bone marrow function. The key, said the lead study author Richard Burt, MD, chief of the division of immunotherapy, is selecting patients with relapsing and remitting MS.

Other studies using stem cell transplantation in patients with MS have failed

to show a benefit because the disease had progressed into a secondary progressive form that is marked by irreversible neurological impairment.

Dr. Burt has been using stem cell transplantation techniques to treat different conditions triggered by autoimmunity. “We are resetting the patient's immune system by taking out the old and putting in the new,” said Dr. Burt, whose latest study on MS appeared online before print on Jan. 29 in *The Lancet Neurology*. “We were looking to reverse neurological disability in these patients, and it appears to have worked, although we must now prove this in a randomized trial.”

Dr. Burt has been working for two decades to understand the immune component of MS. He contends that stem cell transplantation will only benefit those patients in the relapsing and remitting stages when it is an immune-mediated inflammatory disease.

The idea of resetting the immune system in patients with autoimmune diseases and certain cardiovascular disorders has been gaining momentum as studies show positive outcomes in some patients. Last year, Dr. Burt and his colleagues published a review article on the technique in the *Journal of the American Medical Association* (*JAMA*). They assessed the risks and benefits in 26 studies using stem cell therapy to treat a range of autoimmune diseases in more than 850 patients.

“While all trials performed during the inflammatory stage of autoimmune disease suggested that transplantation of hematopoietic [formation of blood or blood cells] stem cells (HSCs) may have a potent disease-remitting effect, remission duration remains unclear, and no randomized trials have been published,” the researchers wrote. At the time of the published *JAMA* study, Dr. Burt and his colleagues were well on the way to finishing a study in

patients with relapsing and remitting MS, which they had begun in 2003.

DR. RICHARD BURT: “We are resetting the patients immune system by taking out the old and putting in the new.”

A REGIMEN OF PARTIAL IMMUNOSUPPRESSION

Unlike cancer therapies that wipe out the entire bone marrow with intense myeloablative regimens, Dr. Burt relied on techniques that do not cause complete bone marrow suppression, lowering the risk of morbidity and mortality. Prior attempts had failed because clinicians treated during the progressive phase of disease using myeloablative methods and the risks were higher, he explained.

Using approaches that require only partial immunosuppression lowers

morbidity, and patients are better able to tolerate the procedure.

The primary outcomes in the study were progression-free survival and reversal of neurological disability three years after the stem cell transplant. Study participants had a relapsing and remitting condition, were between 18 and 55 years old, and had benefited from at least six months of interferon beta, the standard immune modulation drug therapy. Treatment failure was defined as two or more clinical relapses with neurological changes treated with methylprednisolone in the previous year, and MRI evidence of active inflammation. Participants were given a complete physical and neurological assessment, including the Expanded Disability Status Scale (EDSS), the Scripps neurological rating scale, the paced auditory serial addition test, and a timed 25-foot walk. The patients also completed a quality of life questionnaire and had baseline MRI of the brain and cervical spinal cord.

To obtain the stem cells, the investigators drew blood from the arms of the patients and sent it through a centrifuge where red blood cells, platelets, and plasma go back into the circulation but mononuclear cells that contain the stem cells are removed. They were then washed and frozen. Two weeks later, the patients were given drugs to knock out the immune component of the bone marrow. Cancer patients have an intense regimen that knocks out the entire immune system, but the idea with MS patients is to use a safer dose of medicines that only knock out the immune component of the bone marrow. Then, the new (stored) population of healthy bone marrow stem cells were infused back into the patients.

Investigators evaluated patients every six months during the four-year study period, using scores from the Expanded Disability Status Scale (EDSS) to determine a worsening or improvement of neurological function. A change of one point on the scale on two separate exams at least three months apart

was used as evidence of a treatment effect.

After an average of 37 months follow-up, 17 of the 21 patients had improved on the EDSS by at least one point. The other four patients had either no change or improved less than one point. Five patients had a relapse after an average of 11 months post-transplantation having showed some improvement in neurological function, Dr. Burt said. But these five patients did not worsen neurologically.

“It is an extremely interesting approach,” said Steven A. Goldman, MD, chief of neurology at the University of Rochester in New York, who was not involved in the study. “It is an evolutionary step over past attempts using stem cell treatments in patients with multiple sclerosis. But the study was small and uncontrolled. It is clear that a larger and properly randomized trial is needed to prove that the technique is indeed promising.”

“The results are much better than one would expect at this point in the disease,” Dr. Goldman added. “It is impressive. And it seemed to have no downside. But it has to be replicated in a large, randomized controlled trial.”

GLOSSARY: STEM CELL TRANSPLANTATION

- **Hematopoietic stem cell transplantation (HSCT)** is a procedure in which progenitor cells capable of reconstituting normal bone marrow function are administered to a patient.
- **Autologous HSCT** involves extracting stem cells from patients, and storing and harvesting them in a freezer. The patients are then treated with drugs to destroy their bone marrow function to grow new blood cells. Their own stored stem cells are then returned to their body, where they resume the

patient's normal blood cell production.

REFERENCES

• Burk RK, Loh Y, Burns WH, et al. Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study. *Lancet Neurol* 2009; E-pub 2009 Jan. 29.

• Burt RK, Loh Y, Kessler J, et al. Clinical applications of blood-derived and marrow-derived stem cells for nonmalignant diseases. *JAMA* 2008;299(8):925–936.

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