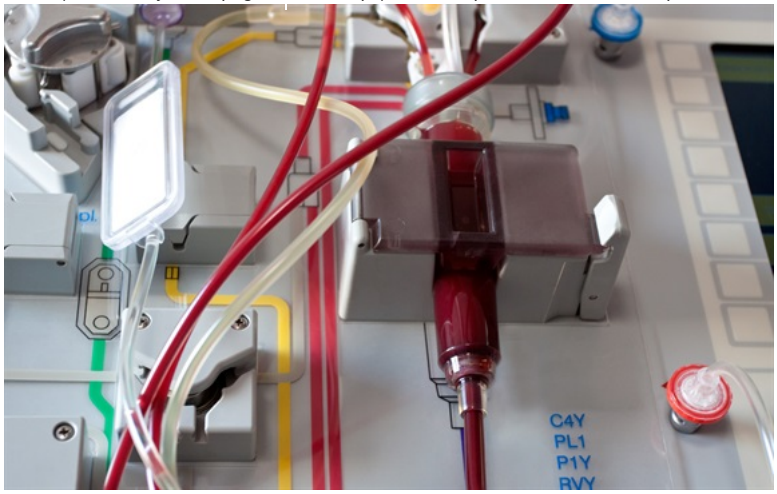

Hematopoietic Stem Cell Transplantation Found Safe and Effective for Patients with Stiff Person Spectrum Disorder

- In the Pipeline (/neurotodayonline/sections/In the Pipeline)

By Ashley Lyles

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The Science Explained

Article In Brief

New research on patients with stiff person spectrum disorder suggests autologous non-myeloablative hematopoietic stem cell transplantation may be safe and effective in a subset of this population. But some experts questioned the use of the procedure given the high-cost of administering the therapy and the variable treatment response.

Autologous non-myeloablative hematopoietic stem cell transplantation (HSCT) was safe and effective in a subset of patients with stiff person spectrum disorder (SPSD), according to a small open-label study, published in the December 14 online edition of *Neurology*.

The beneficial effect of HSCT was variable, however, and tended to improve only in those who had episodic spasms, normal tendon reflexes, and abnormal spinal but normal limb EMGs while on anti-spasmodic medications. It also was beneficial to those who were not taking selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). No patient with lead pipe rigidity responded to treatment.

SPSD is a rare neurological disorder that leads to persistent rigidity and stiffness. Occasional painful muscle spasms vary in frequency and become more frequent in serious cases and are often inducted by increased startle responses to touch, anxiety, and noise, the authors noted.

SPSD may stem from immune-mediated loss of gamma-aminobutyric acid (GABA) inhibitory neurotransmission contributing to aggressive and unchecked neurostimulation, the authors noted. It is generally linked with numerous autoantibodies that impair transport, release, or production of the inhibitory neurotransmitter GABA; the most common autoantibody is focused on glutamic acid decarboxylase, they added.

“I was originally trained in hematology/oncology and transplant leukemia, but 30 years ago I came up with the idea of doing this in autoimmune diseases,” the lead study author Richard K. Burt, MD, professor of medicine in the division of immunotherapy and autoimmune diseases at Northwestern University in Evanston, IL, told *Neurology Today*. “It's modifying the basic training in transplants for leukemia to autoimmune disease.”

“People think this [HSCT] is some sort of stem cell therapy. It absolutely is not that. It's an immune-based therapy,” said Dr. Burt. “It is just a method of re-establishing the cell's tolerance as a one-time treatment,” he added.

“What makes it different than all the other drugs that are immune-based is that this is a one-time treatment and then you get off every other drug,” Dr. Burt told *Neurology Today*.

This approach is essentially resetting the immune system, he added.

Prior research on HSCT has focused on multiple sclerosis and neuromyelitis optica, Dr. Burt said. A randomized trial of HSCT for relapsing remitting multiple sclerosis found the transplant was superior to continued disease-modifying therapy. But, he noted, that prior studies found HSCT does not benefit some patients with secondary progressive MS in the neurodegenerative phase of MS.

"While the pathophysiology [of SPS] is thought to be immune-mediated, despite current immune therapies, the clinical course is often progressive, and autopsy of participants in the later stages of disease may demonstrate neuronal loss, which raises the possibility of a late neurodegenerative phase in which HSCT would be ineffective," he and his colleagues wrote.

Study Details, Findings

Dr. Burt and said the primary endpoint for the trial was safety and National Cancer Institute common toxicity criteria for adverse events during HSCT.

They evaluated 23 participants, whose mean age was 48 years; 91 percent were women. They excluded people whose MRI showed another possible confounding etiology. They included those with a clinical diagnosis of SPSD with painful muscle spasms, axial muscle stiffness, who were between 18- and 60-years old, had anti-GAD antibody in the peripheral blood and/or CSF, co-contraction in opposing limb agonist antagonist muscles, and/or simultaneous electromyography (EMG) verification of continuous paraspinal muscle activity.

Patients underwent an initial evaluation, during which they met with a research nurse and physician, to assess risks and to review the procedure protocol. Patients then had pre-transplant testing to gather baseline data and to ensure that patients meet inclusion criteria.

To help mobilize stem cells into the blood, patients spent one night at the hospital during which they received intravenous cyclophosphamide followed by outpatient injection of granulocyte colony stimulating factor. Ten days later, patients underwent the stem cell harvest via an apheresis machine—a two to four hours process done in the outpatient setting.

Approximately two weeks later, the patients were admitted for HSCT. The overall stem cell transplant stay in the hospital is about two weeks. The initial five days are for a conditioning regimen, consisting of chemotherapy and biologics to eliminate the old immune system.

The immune ablative regimen consisted of intravenous cyclophosphamide administered at 50 mg/kg each day on days two to five prior to stem cell infusion. Patients also received 0.5 mg/kg of rabbit anti-thymocyte globulin on day five, 1.0 mg/kg of rabbit anti-thymocyte globulin on days four and three, and 1.5 mg/kg on days one and two. They were given 1000 mg of rituximab.

Patients received their HSC cells back through a PICC line on day zero—about a 20 to 30 minute process. After the transplant, patients had daily blood draws to evaluate red blood cells, white blood cells, and platelets. Patients received blood, antibiotics, and platelet transfusions as needed. Around day nine or 10 after stem cell infusion neutrophil counts recovered and patients were ready for discharge.

The investigators used quality of life measures on scales and a greater than or equal to 50 percent discontinuation or decrease of anti-spasmodic medications as a basis for their assessments.

No one died from the procedure; however, one year after transplant, a participant died from disease-related progression. Notably, 26 percent did not respond to the therapy, but 74 percent of participants responded, and 47 percent have stayed in remission for an average of 3.5 years.

"This therapeutic intervention requires a multidisciplinary team of experts and could be cost-prohibitive for many patients, especially with such a variable treatment response."—DR. SCOTT NEWSOME

Those who responded to the therapy were less likely to have EMG-documented simultaneous contraction of antagonist/agonist limb muscles (66.7 percent versus 5.9 percent) and lead pipe rigidity (66.7 percent versus 0); nonresponders were less likely to have positive cerebrospinal fluid anti-GAD serology (85.7 percent versus 33 percent), pretransplant intermittent muscle spasms (94 percent versus 0), and normal reflexes (70.6 percent versus 0).

Nine of twelve patients who used SSRIs or SSNIs before undergoing HSCT never responded or relapsed compared with none of 11 responders who never relapsed.

Dr. Burt said, "Limitations to the study were that they had to retrospectively data mine to get an idea of which type of patients with SPSD responded, and that the study involved a single center and will need to be confirmed by others, so that in the future physicians can target the right subset of patients for a highly effective, but also a potentially dangerous therapy."

"Our data based on the patient records tend to point toward which subset respond, but obviously, it is going to take more work and study of this rare disease to confirm that," said Dr. Burt.

Expert Commentary

The best candidates for this procedure are yet to be determined, said Scott Newsome, DO, MSCS, FAAN, FANA, associate professor of neurology at Johns Hopkins University in Baltimore, who was not involved with the study.

"This study suggests that patients who have intermittent spasms, lack of limb rigidity/hyperreflexia on exam, negative limb EMG, and presence of anti-GAD65 antibodies in serum and CSF might benefit the most. Since SPS is a heterogeneous disease that has limited biomarkers of disease burden and treatment response, caution is needed when determining whether an intervention is truly successful."

"This therapeutic intervention requires a multidisciplinary team of experts and could be cost-prohibitive for many patients, especially with such a variable treatment response," Dr. Newsome told *Neurology Today*.

"I have never used it, and I have never recommended it to any of my patients so far because it is an aggressive procedure and it is a last resort when the patients don't respond to the drugs that we have," said Marinos C. Dalakas, MD, FAAN, professor of neurology at Thomas Jefferson University in Philadelphia, who also wrote an accompanying editorial on the study.

For patients with active disease who do not respond to existing therapy and are highly symptomatic, you can consider trying a new approach, especially since in experienced centers safety has improved, noted Dr. Dalakas.

Dr. Dalakas pointed out that the limitations of the study include that the researchers did not try to determine if the patients have active disease by discontinuing IVIg to see if they worsen. In addition, he had concerns with the descriptive correlations in responders and nonresponders as they relate to tendon reflexes, spasms, and quality of life.

"Second, the quality of life measures improved in all the patients, responders, and nonresponders, which indicates a strong placebo effect. The third limitation involves some data mining analysis they did based on tendon reflexes and intermittent spasms because these fluctuate in a "minute to minute phenomenon," said Dr. Dalakas.

Disclosures

Dr. Burt did not report any conflicts of interest. Dr. Dalakas disclosed he received an honorarium for serving on the data and safety monitoring board for the Dysimmune Disease Foundation, and for serving on the editorial board of TAND and N_2. Dr. Scott Newsome has received consultant fees for scientific advisory boards from Biogen, Genentech, Bristol Myers Squibb, EMD Serono, Greenwich Biosciences, Novartis, is an advisor for BioIncept and Autobahn, a clinical adjudication committee member for a MedDay Pharmaceuticals clinical trial and has received research funding (paid directly to institution) from Biogen, Novartis, Genentech, National Multiple Sclerosis Society, Department of Defense, and Patient Centered Outcomes Institute.

Link Up for More Information

• Burt RK, Balabanov R, Han X, et al. Autologous hematopoietic stem cell transplantation for Stiff Person Spectrum Disorder: A clinical trial https://n.neurology.org/content/early/2020/12/14/WNL.0000000000011338 (https://n.neurology.org/content/early/2020/12/14/WNL.0000000000011338). *Neurology* 2020; Epub Dec 14.

• Dalakas MC. A HSCT trial in stiff person syndrome: Limited benefits halt enrollment but should there be more to come https://n.neurology.org/content/early/2020/12/14/WNL.0000000000011349 (https://n.neurology.org/content/early/2020/12/14/WNL.0000000000011349). *Neurology* 2020; Epub Dec 14.

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